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Rational Cancer Chemotherapy

C. P. Rhoads

Sloan-Kettering Institute for Cancer Research, and
Department of Biology and Growth, Sloan-Kettering Division,
Cornell University Medical College, New York City

THE DEVELOPMENT OF CHEMICAL MEANS for restraint of neoplastic disease has passed through two well-defined phases. It is now entering a third. The first is marked by the discovery of agents, or procedures, which cause atrophy of specific tissues and, by virtue of this property, induce restraint of neoplasms derived from them. The hormonal treatment of cancer of the prostate, breast, and of leukemia is, of course, of this first type, as in the use of the radioactive isotopes of phosphorus and iodine.

The second phase is the one of the use of compounds which probably are injurious to cells in direct ratio to their rates of growth. Since many, but not all, neoplastic cells are actively reproducing, they are particularly susceptible. The compounds related to the nitrogen mustards and those acting as antimetabolites to folic acid presumably are in this group.

The third phase has just been entered with the study of substances which injure selectively by virtue of biochemical specificities of the target cells, characteristics which distinguish the neoplastic from their normal analogues growing at the same rate. This selective effect may well be truly specific cancer chemotherapy, now just in its earliest inception, but bright with promise for the future. The compound recently described, 6-mercaptopurine (*1–4*), represents perhaps a first step in the attainment of compounds with selective anti-neoplastic action in man. This possibility is particularly apparent when the results of use of the compound are considered together with the investigative work which led to its synthesis, and with an understanding that related compounds, acting even more selectively by similar principles, are already coming to the testing laboratory.

The compound, 6-mercaptopurine, is the product of a program instituted in 1946 in the laboratories of the Sloan-Kettering Institute. Subsequently, affiliations for complementary work were developed in the Burroughs Wellcome and Company (U.S.A.) Incorporated and the Southern Research Institute. The program was established under five divisions, with functions as follows:

1. The discovery, development, and use of precise methods of assay for measuring the ability of compounds to restrain selectively the growth of mutant as compared to normal cells—viral, bacterial, protozoal, and mammalian. The mutants include, of course, neoplastic cells of animal and human origin.

2. The synthesis, collection, coding, testing, and compilation of results of trial of candidate compounds for cancer chemotherapy.

3. The development of methods for assessing exactly the ability of substances tested to restrain cancer in man.

4. The organization of an extensive program for the application of these methods to patients of suitable types and in adequate numbers, with the training of qualified personnel to real competence in this exceedingly difficult field. It is difficult because it requires the study of desperately ill individuals, a thorough knowledge of the natural history of the various types of cancer, and a complete understanding of the pitfalls inherent in a therapeutic program dealing with a disease often slow in its progress and prone to unpredictable modifications of its course.

5. An orderly program for the comparative analysis of the patterns of nucleic acid anabolism in normal and mutant cellular forms, including the neoplastic in mammals. This work has been notably productive in its yield of new compounds and unique information.

Chemotherapy of bacterial disease came about almost entirely as the result of empiric study. Knowledge of the mechanisms of the chemotherapeutic effect was secondary—the consequence of the availability of selectively acting agents, rather than their source. The empiric approach is at best hazardous, ponderous, and cumbersome. It is one which involves many gambles at high odds. As a result, it is never popular, even though medical history is studded with notable examples of its success. Its first use, in bacteriology, was feasible because of the relative simplicity of the problem and the ease of the manipulations involved in its solution. The number of tests with bacteria that can be made in a given time is limited only by the funds available and the energy of the investigator. The organism whose destruction is sought is capable of artificial cultivation on any scale.

The situation in cancer chemotherapy is quite different, however. Here, though the target, the cancer cell, is well enough defined, it exists in many different forms, each obviously with its own biological characteristics. Furthermore, human cancer has been, until recently, impossible to cultivate outside the body.

Despite all these difficulties, many apparently insurmountable, an empiric attack on cancer was undertaken in our laboratory under Stock (*5*), employing a variety of transplantable animal neoplasms and transferring the results of their study to man as rapidly as possible. This program slowly developed information

which now permits the limited extrapolation of the results of animal tests to palliative cancer therapy in human beings.

To make the program properly inclusive and so as effective as possible, the empiric approach was amplified by the development and application of analytical methods for the comparative study of nucleic acid synthesis in normal and mutant forms. The results have accelerated the empiric work greatly and yielded new principles which appear to provide a rational approach to cancer control.

When the study of nucleic acid metabolism was instituted in 1946 by Brown, little information existed on the anabolism of nucleic acid in any cells, particularly the mammalian. The single experiment reported, that of Plentl and Schoenheimer (*6*), employing N^{15}-marked guanine, had failed to reveal any uptake of this substance by the nucleic acid of the rat. As a consequence, it was generally assumed that such dynamic equilibrium as existed in the case of nucleic acid depended upon purine and pyrimidine synthesis entirely from small, ubiquitous precursors, such as formate and glycine, widely distributed throughout the body. It was further assumed, since the amounts of desoxyribose nucleic acid (DNA) per cell, irrespective of type, were the same, that they were also identical, both in composition and in anabolism, in different cells.

The development of the one-gene, one-enzyme hypothesis, however, by Beadle (*7*) and his associates, gave rise to some consideration of the possibility that cells of different characteristics, and so certainly having different genes, might have DNA of different composition in those genes. Because of the minute size of the gene in comparison to the whole chromosome, the possibility of employing these conceivable differences to develop a chemotherapeutic approach (the selective destruction of certain cells while sparing others) was not at first considered seriously. It remained for the observations of Avery and his co-workers (*8*) to provide unequivocal evidence of the specificity of DNA. This, in turn, established a firm foundation for the development of selectively toxic compounds.

The original demonstration was the classic one, that a pure DNA prepared from Type III virulent, encapsulated pneumococci would transform the offspring of Type II avirulent, unencapsulated pneumococci into the encapsulated forms from which the DNA had been derived. Furthermore, this transformation was permanent, an hereditary characteristic capable of being transferred from parent to offspring indefinitely. Since this original demonstration, the same principle has been shown to obtain for a variety of bacteria and probably for at least one pair of viruses. Clearly, in these instances the DNA capable of transforming is different from that in the organism which is transformed. This difference, it was thought, should be susceptible to chemical definition, and might be reflected in measurable anabolic dissimilarities between the two.

Clearly, two means for defining the heterogeneity of nucleic acid exist. One involves the demonstration of different compositions of DNA's of two sources, preferably those capable of exerting different effects, such as two transforming factors. The other is the proof of unequal rates of incorporation of the same precursor into different DNA's and different DNA fractions. The methods for defining nucleic acid composition in terms of purine-pyrimidine ratios are still not entirely satisfactory. Such data as have been advanced in support of differences in such ratios between cells of different types are suggestive, but still equivocal. Perhaps the most conclusive are those of Markham and Smith (*9*) for different strains of tobacco mosaic virus. Similar data have recently been advanced for two strains of rickettsia (*10*).

The recently reported discovery of two types of DNA by Bendich (*11*) and variations between different tissues in their content of these two types lends further weight to the thesis of cell-specific DNA constitution and anabolism. Such specificity should be tantamount to susceptibility to selective destruction by antimetabolites. The heterogeneity of DNA, which is so essential to the chemotherapist if he is to have a rational program, seems now to have been established beyond reasonable doubt. Furthermore, new data supporting this conclusion are now coming forward from many different laboratories. Most impressive is the recent demonstration by Brown and Watson (*12*), based upon the original publications of Bendich (*11*) and Cavalieri (*13*). Clear proof is presented that a differential binding of nucleic acid bases exists, since different nucleic acids yield different patterns of dissolution by graded concentrations of salt.

The data of Bendich (*14*) on the differential deposition in DNA of the carbon from administered carbon-14 formate are particularly impressive. Not only is the distribution of the tracer different between the two DNA's of different organs, but the entire uptake pattern seems to be characteristic for the particular tissue involved.

The second type of work has been more productive. It is based on the original demonstration by Brown and his associates (*15*) of the recovery of parenterally administered marked adenine in both PNA and DNA of mammalian tissues. This is the point of departure for a substantial part of the many studies presently under way, notably by Mitchell and Skipper (*16*). It was quickly followed by proof from Brown that the mouse differs from the rat in that it will incorporate guanine to a greater extent (*17*). Then came the evidence that the adenine uptake is strikingly different for different types of cells of the same species (*18*). This point was amply supported by studies from many laboratories indicating that mutant strains of bacteria differ radically in their purine and pyrimidine requirements.

The analogy between original (wild) and mutant strains of bacteria, and normal and mutant mammalian cells with neoplastic properties, is obvious. The ability selectively to kill mutant bacteria by withholding from the medium a purine required by mutant and not required by the parent original forms is well established. Though few regarded this ability as the

analogue of a foundation for effective cancer chemotherapy, it became the basis of the work in our laboratories. It led to an extensive program for the synthesis and test of candidate chemotherapeutic compounds there, and also in a number of cooperating units, notably by Hitchings[1] of Burroughs Wellcome and Company (U.S.A.) Inc. and Skipper of the Southern Research Institute. Extensive series of compounds were prepared as modifications of known or presumed precursors of nucleic acid, and studied, with a variety of assay techniques, by Stock, Philips, and co-workers (*5, 19*). The publications of Biesele (*20–22*) should be consulted, since many of the most outstanding results were achieved by this investigator.

One compound, 2,6-diaminopurine, studied almost simultaneously in the Burroughs Wellcome and Sloan-Kettering Institute laboratories, proved to be selectively injurious in tissue culture for certain neoplastic cells of animals as compared with normal cells growing at the same rate (*22*). This was the first proof that such a selective effect, even *in vitro*, could be achieved employing cells of equivalent rates of growth. It is of especial interest that this compound is actually incorporated into normal nucleic acid purines. Not only did the compound exert preferential toxic effects *in vitro*, but it was shown by Burchenal (*23*) to be therapeutically active *in vivo* in prolonging the survival time of mice with certain strains of experimental leukemia.

It has actually been possible indeed to destroy selectively a viral-like, intra-cellular particle, the kappa particle of "killer" paramecia, without destruction of the protozool cell containing it (*24*).

Another product of this program, 8-azaguanine, was studied in several laboratories. In Kidder's hands (*25*) it was found to be active in restraining the growth of certain animal neoplasms, particularly the mouse mammary adenocarcinoma EO 771, although Sugiura has shown it to be inert against other neoplasms (*26*). The studies of Biesele demonstrate beyond question the extraordinary specificity of the effects which can be exerted upon cells of different types by analogues of nucleic acid precursors and by numerous related compounds. Furthermore, they prove that certain types of substitutions in these analogues confer upon the compounds a higher degree of selectivity than do others. This was not only a scientific accomplishment of moment, but it also represents the surmounting of a particularly difficult and frustrating psychological hurdle to cancer chemotherapy. This was the widespread conviction that the selective destruction of cancer as compared with normal cells was impossible, since both had a common origin. The obstacle is now removed by the weight of evidence, and, we hope, for all time. It appears that the way to more effective cancer chemotherapy is open, though it may prove to be a long and arduous one.

The fact of predominant nucleic acid synthesis *de novo* and the possibility that many different pathways exist have been advanced in deprecation of efforts to achieve cancer chemotherapy by block of nucleic acid synthesis. These do pose problems, but there is no reason to regard them as insurmountable. Goldthwait and co-workers (*27*) advanced unequivocal evidence that antimetabolites of folic acid block effectively *de novo* synthesis from formate at least in normal mammalian cells. The acquisition of resistance to and eventual dependence on 8-azaguanine by a transplantable neoplasm studied by Skipper (*28*) is clearly associated with a lessened dependence on *de novo* synthesis and 100 times greater uptake of the C^{14} marked antipurine.

The whole concept of specific cancer chemotherapy depends upon the existence of specific anabolic patterns for nucleic acid by particular cell types including the neoplastic. There is good evidence that these exist for normal cells, although they will unquestionably turn out to be much more complicated and so presumably much more varied and specific than present methods permit us to define. Different, and so useful, specificities will undoubtedly be found to exist for different types of neoplasms. This has also been advanced as an argument by those who oppose work in cancer chemotherapy. The most pessimistic pronouncement on this point is one recently made that 1000 different agents will be needed for 1000 different kinds of cancer. This is unlikely, since perhaps the majority of the cancer deaths are due to disease of a few general types. Data already existing on human therapy indicate that the responses by minor variants within these types tend to be similar, even though not identical.

The crucial question is whether a particular cancer does differ substantially from normal tissues in its requirements for building blocks of nucleic acid, precursors which may be modified to act as antimetabolites. Skipper (*29*), in a most significant contribution, seems now to have answered this question. The animal and human cancers studied for their uptake of C^{14} guanine differed consistently from normal tissue and from each other. Each seems to have its own consistent and specific requirements.

The most recent product of this program, 6-mercaptopurine, has now been in general use since January 23, 1953. On that date it was distributed, with information concerning its use in the treatment of acute leukemia, to several of the leading clinical groups in the country. The experience with it has been now reported and evaluated. The substance, though not curative, is useful indeed. Let us hope that future results with compounds developed on a similar basis, for the treatment of other neoplasms, are as encouraging. Many now ill to death hope for surcease, and many will in the future be grateful for similar hope.

Different rates of uptake of the same precursor by different types of cells clearly have been established. Analogues of these precursors have been synthesized. Certain of them have shown the ability selectively to injure neoplastic as compared with normal cells *in vitro* and *in vivo*. The program has now been extended into related areas by other laboratories, notably those of Woolley (*30*) and Gellhorn (*31*). It will be sur-

[1] Aided by the C. F. Kettering Foundation.

prising indeed if these principles and these compounds with their congeners do not yield new means for cancer control in man within the foreseeable future.

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The Fine Structure of Cellulose Microfibrils

A. Frey-Wyssling

Laboratory of General Botany, Swiss Federal Institute of Technology, Zürich, Switzerland

THE microfibrils detected in native cellulose with the electron microscope (*1, 2*) can be further disintegrated by means of ultrasonics (*3*), hydrolysis (*4*), or oxidation (*5*). Whereas the microfibrils show diameters of 150–250 A, the resulting elementary fibrils (or micellar strands) grade down to 90–70 A. Vogel (*6*) has found that these elementary fibrils are flat filaments, sometimes only 30 A thick. These ribbons anastomose laterally with each other. Their lateral aggregation is visible when ultrathin sections of ramie fibers are disintegrated in a blender. The plane of the ribbon must correspond to the (101) plane of the cellulose crystal lattice, since Mukherjee and Woods (*7*) find by x-ray analysis that cellulose particles of ramie and cotton produced by H_2SO_4 hydrolysis sediment are parallel to that plane.

Based on these facts, the amicroscopic[1] structure of a microfibril can be described by Fig. 1. It represents the cross section of a thin microfibril which is composed of several aggregated elementary fibrils (micellar strands).

The elementary fibrils consist of a crystalline core that is flattened parallel to the (101) lattice plane. This shape is due to a faster growth of the (101) plane, which is more hydrophilic (*8*) than the more slowly growing $(10\bar{1})$ plane. Therefore, more energy is needed to remove the hydration water from the (101) plane when adding a new layer of chain molecules. The crystalline core of the microfibrils is embedded in a cortex of paracrystalline cellulose (*9*). The insufficient order of the chain molecules in this cortex may be caused by the escaping water released on the occasion of the polymerization of glucose and the crystallization of the resulting chain molecules.

The paracrystalline cellulose is responsible for the aggregation of the elementary fibrils to form *microfibrils*. The tendency toward aggregation in the (101) plane is greater than perpendicular to it. As a result,

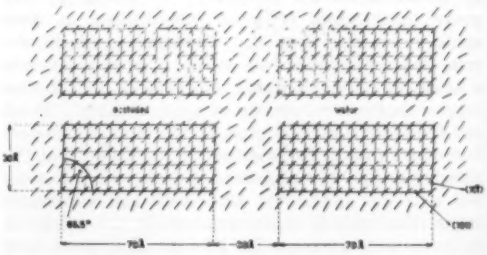

FIG. 1. Section across a microfibril of native cellulose composed of four elementary fibrils or micellar strands. A core of crystalline cellulose chains, seen in cross section, is embedded in paracrystalline cellulose. (101) and $(10\bar{1})$ planes of crystal lattice.

[1] *Amicroscopic*, particles less than 50 A, not visible in even the electron microscope.

water may be occluded between (101) planes. Therefore, the microfibrils are laminated and easily split parallel to the (101) plane, whereas the micellar strands adhere laterally to each other. In this way, broad aggregated ribbons can be formed, as demonstrated in the electron microscope (*10*).

The paracrystalline cellulose and the clefts parallel to the (101) plane are the places where water is adsorbed when cellulose fibers swell. Also, iodine may penetrate between the layers of the microfibrils.

It has been shown (*11*) that, besides these amicroscopic inhomogeneities, there are much coarser submicroscopic capillaries in cellulose fibers which are accessible to colloidal dyestuffs. Those spaces are situated between the microfibrils. They may contain other cell-wall substances and must be considered as channels by which the living cytoplasm receded after the formation of the microfibrils.

The model presented in Fig. 1 is in accordance with the following physical data measured on cellulose fibers. The x-ray analysis of the diameter of the cellulose crystallites yields about 50 A (*11*). Since the cross section of the crystalline area is not isodiametric but is a flat rectangle of about 30×70 A^2, the value 50 A represents a mean value. This mean results from the circular arrangement of the flat elementary fibrils, which have their (101) plane oriented parallel to the lumen of the fiber cell.

The density of crystalline cellulose is 1.59, whereas that of pure fiber cellulose reaches only 1.55 (*12*). Since the void of the submicroscopic capillaries in the fiber cell wall is eliminated when the density is measured, this difference of 0.04 must be due to unorderly crystallized (paracrystalline) cellulose.

Hermans and Weidinger (*13*) find that the so-called crystallinity derived from x-ray scattering is only 70 percent in native fibers, while 30 percent of the cellulose is said to be "amorphous." Since in the electron microscope no such amorphous cellulose can be detected, but only microfibrils and elementary fibrils, the amorphous cellulose must be located inside the microfibrils and therefore be identical with our paracrystalline cellulose. Our model shows that at least a third of the cellulose chains must be paracrystalline when the surface of the elementary fibrils is covered by slightly disordered chain molecules. If the crystallinity is derived from the resistance to hydrolysis (hydrolysis velocity), at least 80 percent is found (*14*). From our figure, it is evident that paracrystalline cellulose chains at the very surface of the crystalline area, although they contribute to the diffuse diffraction of x-rays, are better protected against hydrolysis than more distant ones. Therefore, the hydrolysis method must yield higher values for the crystallinity than the x-ray diffraction.

In primary cell walls (*1*) and plant slimes (*15*), the microfibrils are clearly individualized, whereas in secondary cell walls, due to the paracrystalline cortex, they aggregate to form coarser bands (*10*), as indicated above. It was open to discussion whether the individuality in the first case is caused by a more compact surface of the microfibrils or only by their considerable distance, since the cellulose component represents but a small fraction in growing cell walls and slimes.

Figure 2 shows how distantly the cellulose microfibrils are situated in a growing primary cell wall before it is freed of all wall substances other than cellulose and dehydrated for examination in the electron microscope. It was of interest to know whether the macromolecular properties of this cellulose in primary cell walls differ from those of the cellulose in such secondary walls of cotton, ramie, and wood. G. V. Schulz and M. Marx in Mainz, and P. H. Hermans and A. Weidinger in Utrecht, were kind enough to determine the degree of polymerization and the crystallinity in cellulose prepared from growing root tips and coleoptiles of corn. The results are shown in Table 1.

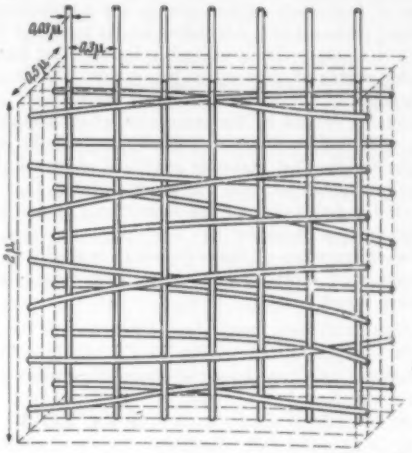

FIG. 2. Texture of the cellulose microfibrils in the growing primary cell wall.

TABLE 1. Cellulose of primary (I) cell walls of *Zea mays* and secondary (II) cell walls of ramie.

	Root tip (I)	Coleoptile (I)	Cellulose fibers (II)
Chemical composition*			
Lipid extract	3.4%	5.3%	—
Alkali extract†	84.5%	89.5%	10%
α-Cellulose	12.1%	5.2%	90%
Degree of polymerization (DP)*	1050	867	> 3000
Crystallinity‡			
Prep. for electron microscopy	57%	59%	
Prep. for DP determination	34%	37%	70%

* By courtesy of G. V. Schulz and M. Marx, Mainz.
† These figures include the protoplasmic contents of the growing cells.
‡ By courtesy of P. H. Hermans and A. Weidinger, Utrecht.

The degree of polymerization of primary wall cellulose seems to be considerably less than that of secondary walls. But it is still good α-cellulose. On the other hand, the crystallinity is astonishingly poor. Dr. Hermans has informed me that only extracellular cellulose of *Bacterium xylinum* has as low a crystallinity as these preparations. According to our model of Fig. 1, the elementary fibrils of such cellulose must have a broader cortex of paracrystalline chains. This insufficient order of the surface layers in the primary wall is probably caused by the large amount of hemicelluloses and pectins, which may hinder an orderly crystallization. The fact that only one-third of its cellulose is really crystalline rules out the possibility that the observed individuality of the microfibrils is due to a better surface delimitation. Therefore, the lack of lateral aggregation of the cellulose microfibrils in the primary wall must be caused by their considerable distance apart (Fig. 2).

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News and Notes

Symposium on the Utilization of Solar Energy

A Symposium on the Utilization of Solar Energy was held at the University of Wisconsin Sept. 12–14. It was sponsored jointly by the National Science Foundation and the University of Wisconsin, with Professor Farrington Daniels acting as Chairman. Attendance was limited to an invited list of 40 people in order that the discussions and exchange of information could be as free as possible; no formal papers were presented.

The general purpose of the symposium was to assess the present knowledge of solar energy and to consider its future. It was hoped that to point out unexplored areas would arouse the attention of those who might be interested in conducting research.

Palmer Putnam opened the conference with a statement concerning the long-range inadequacy of the world's resources of coal, gas, oil, and uranium. At the present rate of fuel consumption, and including the projected increase over the near future, it was estimated that the supply of easily obtainable (i.e., at a cost not more than twice present prices) coal, oil, and gas would be exhausted in less than 100 years. The nuclear fuels would only last another 150 to 200 years. Therefore, it was felt that this generation would be negligent in its duty to posterity if research in the utilization of solar energy were not quickly accelerated.

The first general discussion on solar energy at the conference centered around its storage and utilization for house heating, water heating, and cooking. This discussion indicated that knowledge of absorbents of solar energy was well advanced, but that considerable improvement was still necessary before house heating with solar energy could be achieved without the use of auxiliary fossil fuels. One of the major problems is the storage of energy through the night and during long periods of overcast or stormy weather. Collection and storage are interrelated and will require much more research, but substantial progress is to be expected in the near future. Improvements in house design would make possible better use of the sun's heat in both winter and summer.

The next question considered was that of solar power. Present knowledge indicated that solar power in small units might be produced in certain parts of the world, including the southwestern part of the United States, at from two to three times the current cost of power production from coal and oil. The chief disadvantage is that the power would be intermittent because it can be produced only during the hours of sunlight. There was some discussion of the possibility of deriving power from engines with water vapor at low pressures, making use of low temperatures. This method seemed farther away than the absorption of solar energy to produce steam, and there were arguments concerning the relative merits of focusing mirrors and black collectors with multiple glass plates.

Closely allied to the power problem is the solar evaporation of sea water. Some progress in this regard has been made by putting dyes in the water in order to improve the absorption of energy. One part per million of dye may increase absorption by as much as thirty percent in the evaporation of water to yield salt.

The question of the production of conventional fuels from agricultural and algal sources was considered briefly. The consensus was that this would be an in-

efficient use of these materials, that they could be used to greater advantage in other ways, and that energy should be produced by more direct methods.

For any widespread use of solar energy, there must be a better understanding of the meteorological implications. If improved methods for protecting crops against frost could be devised, and the growing season thus lengthened, the food supply in certain areas of the world could be increased appreciably. Conversely, if absorption could be induced on snow surfaces so that melting would be speeded, the ground would be available for planting sooner in the spring. Meteorology could make an important contribution to the advancement of solar energy by developing an improved method for specifying the amount of solar radiation at any given point on the globe. Expensive shields and ditches are now being used in California to conserve solar radiation and to influence wind currents so as to minimize frost damage.

Solar energy is also being used to heat to high temperatures certain materials whose contamination must be prevented. By means of solar furnaces that reach a temperature of over 4400° C, the heat conduction and thermal shock of high-melting ceramics can be studied.

The conference gave attention to those areas that show the greatest promise of making major contributions to the utilization of solar energy as a source of power in the future, both from the short-range view in which solar energy competes with present fuel supplies, and from the long-range view of the time when fuel supplies will have been greatly depleted and the sun's energy will have to be used more directly. Chemists should be urged to search for a suitable solar compound which will absorb sunlight through photochemical reactions, store the energy, and then release it at will in a way suitable for practical use. To find such a chemical compound presents a real challenge, but basic research on the question should be encouraged. When more is known about the fundamental principles involved, there will be a better chance of finding such a compound. The use of sunlight in photochemical reactions offers theoretical advantages over its use as heat in engines. However, one of the difficulties is that the products of these photochemical reactions may immediately react and reverse the reaction.

An example of a possibly useful photochemical reaction is the production of hydrogen and oxygen from water, using cerium salts as the absorbent to transfer the energy needed to make the water dissociate. The hydrogen and oxygen could be stored and later recombined to give back the stored energy. Another possibility is the absorption of energy by one side of a photovoltaic cell or an electrical battery while the second side of the cell is kept in darkness. The side absorbing the energy from the sun would transmit that energy through an electric circuit to the side which is kept in darkness.

Still another means of utilizing solar energy was suggested by the same direct electrical method. It was felt that, in addition to studies of the kind mentioned above, considerable more work should be done on the thermo-element method, in which two different electric conductors are connected, with one junction heated by the sun and the other junction kept cold. The resulting current could be made to do work; however, it will be necessary to find metals or alloys that, when connected together in this way, will produce substantially higher voltages than any produced so far.

Nature's own method of utilizing solar energy in growing plants through photosynthesis is a remarkable phenomenon which can guide us in our approach to the collection of solar energy. We are just beginning to understand photosynthesis. Green chlorophyll absorbs light and decomposes water to give hydrogen. This reduces carbon dioxide, resulting in organic material (carbohydrates) that can be preserved. The organic fuels then recombine with the oxygen of the air to release the energy as needed. The energy-absorbing material, and the mechanisms for preventing the reverse reaction and for storing the energy, set a pattern which should be studied further. Perhaps eventually the same type of reaction may be produced artificially, without any requirement for the growing plant and good soil conditions.

Considerable attention was given to the possibilities of a "poor man's solar engine." Atomic energy requires central stations with large capital investments but, theoretically, small solar engines could be placed in out of the way places. Although such engines would be inefficient thermodynamically and economically in comparison with modern engines, they might find extensive use, particularly in countries which are not industrialized. The night interruption of power would not be a disadvantage in operations such as the pumping of water for irrigation.

No great achievements of practical value were reported in this attack on the problem of utilizing solar energy, and it was generally agreed that no new era of direct utilization of solar energy is yet in sight. However, many of the participants of the conference, including architects, engineers, chemists, and meteorologists, were pleased to find that such substantial progress is being made in the preliminary development of solar house heating, solar power production, evaporation of sea water, and in the application of meteorology. They were also interested to discover that there are many areas of physical chemistry, physics, and engineering where fundamental research may well lead to significant advances in this direction.

FARRINGTON DANIELS

Department of Chemistry
University of Wisconsin

RALPH MORGEN

Program Director for Engineering
National Science Foundation

Science News

To study the effects of mechanical vibration on man, the Navy has designed and constructed a research instrument termed a large **displacement-amplitude vibration machine.** The Naval Research Laboratory, cooperating with the Naval Medical Research Institute, has completed the first phase of the project by the construction, calibration, and testing of the instrument. The instrument, which has taken over five years to build, has now been assembled and installed at the Naval Medical Research Institute.

The two-ton instrument was designed to study low frequency vibrations. It is capable of producing smooth vibrations from two to 50 cycles per second. Constructed to handle loads up to 200 pounds, the table-top vibrating platform moves vertically through a maximum of four inches at accelerations up to 15 units of gravity. Also, special built-in features allow the investigators to vary the cycles per second and the amplitude while the instrument is in operation, or to hold one and vary the other.

After an extensive study, E. M. Brooks of St. Louis University predicts that the best spot for viewing the **eclipse of the sun** next June 30 will be Minneapolis. There the early morning sky is less often overcast and the air is relatively dry. Nevertheless, the chance that the eclipse will be visible from Minneapolis is less than 50 percent. At other spots along the total eclipse path the chances of good observing weather are even less.

Seven of the most accessible sites were investigated. Totality will be visible in the United States across an area running from northeastern Nebraska across South Dakota, Iowa, Minnesota, Wisconsin, upper Michigan, and the provinces of Ontario and Quebec in Canada before passing over the Labrador coast. The sites considered were Spencer, Iowa; Minneapolis; Park Falls, Wis.; Calumet, Mich.; and White River, Kapuskasing, and Moonsonee, Ontario. Park Falls was found to be the best for photographing the eclipse, although Minneapolis offers a better opportunity for visual observations.

Foreign scientists are now conducting much of the chemical research in large American universities that ordinarily would be done by Americans, Professor Roger Adams of the University of Illinois stated recently. Attributing this situation in great part to the operations of the American selective service system, he said:

"If the current attitude of the draft boards towards scientists continues, important research developments in our universities will be achieved almost exclusively with the help of foreigners."

It is significant, he noted, that even now "only 25 to 50 percent of the postdoctoral research assistants in institutions with large research programs, such as Harvard, the Massachusetts Institute of Technology, and the University of Illinois, are Americans."

The Council of the Federation of American Scientists has issued the following statement regarding **prospective appointments to the National Science Board.**

On May 10, 1954 the terms of office of eight members of the National Science Board, established by the National Science Foundation Act of 1950 as the policy-making group for the Foundation, will expire. Reaffirming its belief, as expressed in the past, that a strong, vigorous National Science Foundation is essential to our continued scientific progress as a nation, the Council urges that the most careful consideration be given to new appointments to the Board. Government officials and scientists and their organizations have joint responsibility to ensure that the nominations presented by the President to the Senate will be of the highest caliber and will give to the Board proper balance and the widest perspective.

The Council believes that, among others, the following principles should be observed in considering nominees:

1. Incumbents whose terms are expiring should be considered individually for renomination on the basis of their past performance and future promise. Blanket renomination of all incumbents, as seemed advisable in 1952, would now both establish bad precedent and fail to take the opportunity to bring new points of view into the Board. For best working relations between the Foundation and the scientific community, continuous exchange of personnel between them is desirable.

2. Nominees to the Board should be distinguished for their breadth of view on the relation of science and public affairs as well as for leadership in their particular specialty.

3. In considering problems of balance within the Board, attention should be given to the proportion of actual working scientists in relation to members engaged mainly in the administration of scientific or other activities. In this connection, it is worth noting that the terms of three of the small number of active working scientists on the 24-man Board expire this year.

4. In relation to problems of balance, also, attention should be given to the appointment of younger individuals, creatively active and close to the problems of training, selection and encouragement of new scientific personnel.

The current size of the **World Health Organization,** which totals 84 nations now that Yemen has signed the constitution, shows that the nations of the world put health above everything except communications. The 84-member WHO is outranked only by the 113-member International Telecommunications Union and the 93-member Universal Postal Union among the specialized agencies of the United Nations. The UN itself numbers only 60 members.

WMO (World Meteorological Organization) now counts 79 members. Next come UNESCO and FAO, each with 68 members, ILO with 66, ICAO (International Civil Aviation Organization) with 59 members, and the International Monetary Fund and International Bank for Reconstruction and Development with 54 members each.

Two other specialized UN agencies are not yet officially in existence, but each has had some nations sign-

ing its constitution. These are the International Trade Organization with 54 signers and the Intergovernmental Maritime Consultative Organization with 11 signers.

Scientists in the News

David Bass, biochemist at the Quartermaster Research and Development Command, Lawrence, Mass., and lecturer in physiology at Boston University, has received the Research Directors' Award for 1953. Dr. Bass was cited for his contributions in directing, supervising, planning, and executing several difficult studies in developing new-type survival rations for military and civilian use in time of emergency. These studies were conducted in collaboration with 1st Lt. Murray Quinn, MC, and 1st Lt. Charles R. Kleeman, MC.

The Institute of Radio Engineers has announced the following awards; presentation will be made at the Institute's annual banquet on March 24 during the national convention:

Alda V. Bedford, RCA Laboratories Division, Princeton, N.J., has been awarded the Vladimir K. Zworykin Television Prize Award for 1954 "for his contributions to the principle of mixed highs and its application to color television." The award is presented annually to engineers who have made the most important contributions to electronic television.

The Institute's Morris Liebmann Memorial Prize, one of the highest awards in the radio engineering field, was bestowed on **Robert R. Warnecke,** Technical Director of Companie Générale de Telegraphie Sans Fil, Paris, France, "for his many valuable contributions and scientific advancements in the field of electron tubes, and in particular, the magnetron class of traveling-wave tubes."

Harold A. Zahl, Director of Research, Signal Corps Engineering Laboratories, Fort Monmouth, N.J., was named the recipient of the Harry Diamond Memorial Award for 1954 "for his technical contributions, his long service, and his leadership in the U.S. Army Signal Corps research program." This award is given annually to persons in government service for outstanding contributions in the field of electronic research.

Howard R. Bierman, formerly associate clinical professor of oncology at the University of California School of Medicine, San Francisco, has assumed his duties as medical and scientific director of the Hospital for Tumors and Allied Diseases at the City of Hope Medical Center, Duarte, Calif. Dr. Bierman will head the extensive program of research, service, and postgraduate medical education in malignant diseases at the new Medical Center.

J. A. Campbell Colston, Editor of the *Journal of Urology,* has been elected president of the American Urological Association.

George L. Cunningham, industrial scientist, and a consultant for the applied science laboratory of the University of Cincinnati, has been appointed to the staff of the Southwest Research Institute in San Antonio.

Air Research and Development Headquarters, Baltimore, have announced the appointment of **Lt. Col. William O. Davis** as chief of scientific research.

Desmond D. Dolan, associate research professor and associate professor of horticulture at the Rhode Island Agricultural Experiment Station, has been named regional coordinator of the newly created Plant Introduction Station of the New York State Experiment Station, Geneva. He will work in close cooperation with the experiment stations of the twelve states that make up the Northeastern Region and with the Division of Plant Exploration and Introduction of the U.S. Bureau of Plant Industry.

Willis A. Gortner, who has been associated with the Bjorksten Research Foundation, Madison, Wis., during his sabbatical leave, has returned to his duties as head of the Department of Chemistry of the Pineapple Research Institute, Hawaii.

Herbert E. Hawkes, recently chief of the Geochemical Prospecting Section of the U.S. Geological Survey, Denver Federal Center, has joined the staff of the Department of Geology and Geophysics at the Massachusetts Institute of Technology as lecturer in geochemistry. Dr. Hawkes will conduct one course in geochemical prospecting and will carry on geochemical research at the Institute.

The Foundation for Research on Human Behavior, recently established in Ann Arbor, has announced the appointment of **Samuel P. Hayes, Jr.,** as its first director. Dr. Hayes formerly headed the Far East programs of the Foreign Operations Administration. The aim of the new foundation is to increase the scientific knowledge of industry, government, and social welfare agencies and to promote the use of this knowledge.

Martin Henze, former director of the Zoological Station of Naples and professor emeritus at the University of Innsbruck, Austria, has been awarded an honorary Doctor's degree in medicine by that university on the occasion of his 80th birthday. Dr. Henze now resides in Pasadena.

Richard Alden Howard, professor and chairman of the Department of Botany at the University of Connecticut, has been named Arnold professor of botany and professor of dendrology at Harvard University. **Reed Clark Rollins,** an authority on plant genetics and director of the Gray Herbarium, will become, in addition, Asa Gray professor of systematic botany. Both appointments are effective Feb. 1, 1954.

Hugh H. Hussey has been appointed professor and head of the Department of Preventive Medicine and Public Health at the Georgetown University School of Medicine. He also becomes a member of the Executive

Faculty of the Medical School. In addition to his new duties, Dr. Hussey will continue his lectures in medicine and clinical chemistry.

Mervin J. Kelly, president of Bell Telephone Laboratories, is to receive the Industrial Research Institute Medal for 1954. The medal is given annually for "outstanding accomplishment in leadership in or management of industrial research which contributes broadly to the development of industry or the public welfare." Formal presentation will be made in San Francisco on April 22.

Jack W. Keuffel, research associate who has been working in the Cosmic Ray group at Princeton University, has joined the Department of Physics, University of Utah, as an associate professor. He will continue his researches on the high energy component of cosmic rays, both at the University and at a field site in the neighboring mountains.

Marcel A. Martin has joined the staff of the Applied Physics Laboratory of The Johns Hopkins University, in Silver Spring, Md. He came to the United States in 1945 as a representative of the French government to make a study in American industries of control testing and optical equipment. Later, he was with the American Optical Company and then the Jacobs Instrument Company.

William J. Morgan, formerly with the Psychological Strategy Board, has been appointed Deputy Chief, Research Branch, Office of the Chief, Psychological Warfare, Department of the Army.

Carl Neuberg of the New York Medical College and the Polytechnic Institute of Brooklyn has been awarded honorary membership in the German Society of Physiological Chemists.

Raphael O. Patt has been named an assistant medical director of the American Heart Association. The staff of the Association's Medical Division now includes two assistant medical directors. Frederick J. Lewy has served in that position since July, 1951.

Geoffrey William Rake, an authority in the field of microbiology, has been appointed research professor of microbiology in medicine at both the School of Medicine and School of Veterinary Medicine, University of Pennsylvania.

John Francis Reintjes, associate professor of electrical engineering at the Massachusetts Institute of Technology, has been appointed director of the Servomechanisms Laboratory of the Department of Electrical Engineering. Dr. Reintjes first joined the M.I.T. staff in 1943.

Donald K. Reynolds, senior research engineer in Stanford Research Institute's Engineering Division, has been granted a three-year leave of absence to serve as professor at the Instituto Tecnologico de Aeronautica, a government-sponsored aeronautical school at San José dos Campos, São Paulo, Brazil. He will teach at the Institute and will conduct research on problems related to military and civilian aircraft.

Herbert Robbins, of the University of North Carolina, has been appointed professor of mathematical statistics at Columbia University.

Emanuel A. Salma, associate professor of mechanical engineering, has been appointed acting director of the Evening Division of New York University's College of Engineering. He succeeds **John A. Hill,** who has resigned to accept a position with the Minneapolis Honeywell Company.

Conley Hall Sanford is retiring as chief-of-staff at the John Gaston Hospital and chief of the Division of Medicine at the University of Tennessee College of Medicine, positions he has held since 1939. Dr. Sanford will continue as professor of medicine and as a private practitioner.

E. P. Vance, chairman of the Department of Mathematics at Oberlin College, is on sabbatical leave for the year 1953–54; R. R. Stoll is serving as acting chairman.

The American Association of Physics Teachers has announced the award of its Oersted Medal "for notable contributions to the teaching of physics" to **C. N. Wall,** professor of physics, University of Minnesota. Presentation will be made during the Association's annual meeting, Jan. 28–30.

Education

Marian College, Indianapolis, is constructing a three-story science building, Scotus Hall. On the first floor will be biology, with a greenhouse and an animal room adjoining; physics will be on the second floor, and chemistry on the third. The building is to be ready for use in September, 1954. At this time the college will begin admitting men students, establishing Marian as the first Catholic coeducational college in the State of Indiana.

Mount Holyoke College is starting construction of a new chemistry building that will cost approximately one million dollars. The north end of the new building will connect directly with the present physics building. Lecture rooms are to be concentrated in the one-story central area of the new structure; these have been designed for use not only by chemistry and physics, but also by the rest of the college for both classes and public lectures. The east wing, containing laboratories, offices, stock rooms, seminar rooms, and a library, will have a second story and also a basement floor. The eight laboratories in this wing will each accommodate a section of 20 to 24 students.

Purdue University's Departments of Biological Sciences and Agricultural Economics have been awarded a joint grant from the Indiana Heart Foundation

to undertake a $130,000 five-year study of the energy requirements of various types of agricultural work in relation to the incidence, causes of, and magnitude of heart disease among rural workers. The objectives of this long range study are: (1) to determine the energy requirements, cardiac output, and other physiological values for a representative sample of rural workers in Indiana and establish norms for this segment of the population by age, type of work, barometric pressure, temperature, humidity, and other environmental factors; (2) to determine energy requirements, cardiac output, and other physiological values as work methods for doing essential farm jobs; (3) to develop and evaluate easier, more effective, and more economical work methods for the cardiac worker through changes in machinery, equipment, layout, work order, and motion patterns; and (4) to formulate job classifications according to energy requirements.

To accomplish these objectives, M. X. Zarrow and associates in the Department of Biological Sciences will supervise tests of agricultural workers of one or more rural areas and make measurements of oxygen consumption, cardiac output, blood pressure, heart rate, muscle fatigue, and vital capacity. A mobile laboratory with the necessary equipment for measuring energy requirements, etc., will be assembled and sent into the field where farmers are working. L. S. Hardin of the Department of Agricultural Economics and Work Simplification will direct the development and evaluation of easier and more effective work methods for the cardiac farmers, according to the energy requirements of the various farm jobs.

Grants and Fellowships

The Hawaiian Academy of Science has awarded **AAAS Research Grants** to: John Forster, Department of Sociology, University of Hawaii, for his project on Samoan communities in Hawaii; and Shirley M. Trefz, Department of Zoology, University of Hawaii, for her study of the digestive physiology of holothurians with reference to their role in the ecology of coral reefs.

The Lederle Laboratories Division of the American Cyanamid Company has announced the establishment of the **Lederle Medical Faculty Awards.** The purpose of the program is to encourage men and women who have progressed beyond the stage of development which is now encompassed by the postdoctorate fellowships, or the so-called senior fellowships, in preclinical sciences. The program will assist promising teachers and investigators, particularly in the fields of anatomy, biochemistry, microbiology, pathology, pharmacology, and physiology, for a limited period with the expectation that the medical schools which have appointed them, or some other schools, will thereafter provide for future support. The plan is also intended to aid departments that could benefit by expansion and offer opportunities for development of promising individuals.

The awards will be administered by an independent committee composed of professors representing most of the preclinical sciences and drawn from medical schools throughout the United States. Direct requests to this committee for the support of specific individuals will be accepted from U.S. and Canadian medical schools through their administrative officers, or from heads of departments with approval of such administrative officers. The curriculum vitae of the candidate, together with information supporting his eligibility, the reasons for requesting the support, and a general outline of the program proposed by the head of the department for that individual, must accompany each request. An independent statement from the individual who is recommended should be sent directly to the committee.

Announcement of the recipients will be made not later than May 1 of each year, commencing in 1954. Candidates must hold faculty rank. Awards will be made for a term not exceeding three years. The only restriction is that the total amount, which will be dispersed at a rate to be determined by the committee, shall not exceed $10,000 in any one year to any one grantee.

The funds should be used primarily to increase or to create salaries for the designated individuals, but they may be used, in part, to support the departmental activities of the individual within the total amount granted. The funds are meant to augment, but not replace, funds already available for the department in question; they are not intended as, and will not be used for, "recapture" funds. While the Lederle Medical Faculty Awards Committee will be interested in the progress of each grantee, no formal reports will be required. Address all communications to: Lederle Medical Faculty Awards, Office of the Secretary, Pearl River, N.Y.

The **American Trudeau Society,** Medical Section of the National Tuberculosis Association, provides a limited number of fellowships to promote the training and development of investigators in the field of tuberculosis and related pulmonary diseases. The awards are open to citizens of the United States for work within this country. Preference is given to candidates not more than 30 years of age who have the degree of Doctor of Medicine or other doctor's degree. Within the broad field of research on tuberculosis, applications will be considered in the special disciplines of clinical medicine and surgery, epidemiology, chemistry, microbiology, pathology, and pulmonary physiology.

Stipends are determined by individual circumstances and may vary from $3000 to $3600 per annum. No other remunerative work will be permitted during the tenure of the fellowship. Appointments are for full-time service and may begin at any time determined by the fellowship board. They are made for one year, but they may be renewed up to a total period of three years. Applications are considered in April or May

and October; *they must be received by April 1 or Sept. 1.* For further information communicate with The Director of Medical Research, American Trudeau Society, c/o Henry Phipps Institute, Seventh and Lombard Streets, Philadelphia 47, Pa.

The **Atomic Energy Commission** awarded 69 unclassified research contracts in the fields of biology, medicine, and biophysics during the period July–September, 1953:

New Projects

University of Connecticut. A. E. Schwarting. Study of the method of ergot formations by use of isotopes.

University of Illinois. S. B. Binkley, College of Medicine. Chemistry and biological significance of nucleotides and polynucleotides.

University of Tennessee. J. D. Perkinson, Jr., School of Biological Sciences. Effect of internal radiation on cellular metabolism.

Vanderbilt University. M. T. Bush, Medical School. Metabolic fate of barbituric acid anesthetics with special reference to evipal.

Louisiana State University. H. E. Wheeler. Investigations of the toxin theory of plant disease using labeled plant pathogens.

Smithsonian Institution. R. B. Withrow. Specific biological indicators of ionizing radiation and the mechanism of its action.

New York University-Bellevue Medical Center. W. E. Smith. Investigation of factors that may modify neoplastic changes induced by irradiation.

Radio Corporation of America. Multiplier phototube development.

Contract Renewals and Extensions

Amherst College. P. T. Ives. Studies of mutations in bacteria and in *Drosophila* induced by radiation.

University of Arkansas. J. Sacks. Studies on the phosphorylation cycle in the intact animal using radioactive phosphorus.

University of Chicago. H. Gaffron. Effect of blue and dark red light upon reactivation of ultraviolet treated photosynthetic microorganisms.

Connecticut Agricultural Experiment Station. P. E. Waggoner and A. E. Dimond. Therapy of plant disease by nuclear radiations.

University of Illinois. B. C. Johnson. Nutritional biochemistry on the metabolism of vitamins and amino acids.

University of Illinois. H. H. Mitchell. Content in human tissues of eleven trace elements.

Indiana University Foundation. H. J. Muller. Influence of radiation in altering the incidence of mutations in *Drosophila.*

Johns Hopkins University. B. F. Chow. Purification of intrinsic factor in gastric juices.

Johns Hopkins University School of Medicine. T. Enns and F. Chinard. Study of relative diffusion rates of isotopes from capillaries.

University of Maryland. J. C. Shaw. Metabolism of radioactive carbon compounds in lactating ruminants.

University of Massachusetts. P. A. Swenson. Effects of ultraviolet radiations on phosphate turnover of yeast cells in the presence of galactose.

Northwestern University. G. H. Mickey. Comparison of the delayed effects produced by chemical mutagens and by x-rays.

University of Notre Dame. C. S. Bachofer. Study of the protection of virus systems against irradiation.

University of Oregon. F. J. Reithel. Investigation of lactose synthesis in mammary gland homogenates.

University of Pennsylvania. D. R. Goddard and W. Stepka. Study of sulfate reduction and the biosynthesis of organic sulfur derivatives in higher plants.

University of Pennsylvania. D. W. Wilson. Synthesis of isotopic carbon compounds used in biochemistry.

University of Pittsburgh. M. A. Lauffer. Study of correlation of radiation effects with physical and chemical changes in viruses.

Purdue Research Foundation. H. Koffler and D. M. Powelson. Physiology of hydrogen bacteria.

Roscoe B. Jackson Memorial Laboratory. E. S. Russell and W. S. Murray. Maintenance of a genetically controlled colony of mice to insure the availability of strains of known constitution to AEC institutions and contractors.

Stanford University. A. C. Giese. Studies on photoreactivation following ultraviolet irradiation injury.

Syracuse University. B. S. Strauss. Study of intermediate carbohydrate metabolism in neurospora using radioactive carbon and biochemical mutants.

Tennessee Agricultural and Industrial State College. H. B. Crouch. Radiation and tracer element studies on certain pathogenic protozoa and nematodes of rodents.

University of Wisconsin. P. H. Phillips. Long time effects of intermittent radiation on dogs.

Yale University. N. H. Giles, Jr. Investigations on the cytogenic effects of radiations.

Boston University. L. C. Wyman. Effect of irradiation on the growth and functioning of transplanted or regenerated adrenocortical tissue in the rat.

The Chicago Medical School. P. Shubik. Study of the latent tumor cells as produced by beta radiation and a comparison of the latent tumor state with that produced by chemical carcinogens.

Columbia University. A. Gorbman. Biological effects of radiation from excessive amounts of radioiodine.

Johns Hopkins University School of Medicine. C. L. Conley. Studies of the absorption, utilization, and excretion of vitamin B-12, using B-12 containing radioactive cobalt (Co^{60}). Synthesis of compounds with vitamin K activity labeled with radioactive carbon (C^{14}) for use in tracer studies.

Johns Hopkins University. J. E. Howard. Investigation of the mechanism of bone deposition and related physiological studies.

Massachusetts General Hospital. O. Cope. Effects of radioactive iodine on biology of the thyroid gland.

Massachusetts General Hospital. W. H. Sweet. External localization of brain tumors employing positron-emitting isotopes.

New England Deaconess Hospital. S. P. Hicks. Effect of ionizing radiation on the developing mammalian nervous system.

New York University College of Medicine. H. W. Smith. Study of body fluid distribution in hypertensive and renal disease and collateral physiological studies.

Northwestern University. S. Freeman. Studies on radiation induced cataracts.

Northwestern University. R. W. Schayer. Studies of the metabolism and biogenesis of histamine.

Peter Bent Brigham Hospital. F. D. Moore. Intracellular changes in trauma, depletion and repair; biochemical studies in the human being with the aid of isotopes.

University of Pittsburgh. F. J. Dixon. Study of the effects of radiation on the immune response with special reference to factors that increase the radio-resistance of the immune response.

Sloan-Kettering Institute for Cancer Research. C. P. Rhoads. Biological effect of radiation, and related biochemical and physical studies.

Tufts College. D. Rapport. Study of the relation of radiation on reactions associated with growth.

Washington University. I. L. Shechmeister. Investigations of the relationship between radiation damage and the immune state.

Western Reserve University. L. A. Manson and L. O. Krampitz. Effect of incorporated radioactivity on the biological activity of bacteriophage.

University of Wisconsin. H. F. Harlow and P. H. Settlage. The effect of various forms of irradiation of the brain on behavior of monkeys and chimpanzees.

Worcester Foundation for Experimental Biology. G. Pincus. Investigation of the effects of radiation on the biosynthesis and metabolism of adrenocortical steroids.

Columbia University. V. K. LaMer. Filtration of monodisperse radioactive solid aerosols (dusts).

Allen B. DuMont Laboratories, Inc. Photomultiplier tube development.

Massachusetts Institute of Technology. R. D. Evans. Radium and mesothorium poisoning and dosimetry and instrumentation techniques in applied radioactivity.

Sloan-Kettering Institute for Cancer Research. J. S. Laughlin. Equivalence of absorbed radiation energy and cavity ionization.

University of Wisconsin. D. M. Angevine and J. J. Lalich. Development and application of historadiography in relation to the distribution of mass and localization of elements in normal and pathologic tissues.

Western Reserve University. H. G. Wood and L. O. Krampitz. Intermediary metabolism of carbohydrates by bacteria.

University of Wisconsin. R. H. Burris and P. W. Wilson. Biological nitrogen fixation with isotope tracers.

University of Wisconsin. R. H. Burris, M. J. Johnson, and

P. W. Wilson. Metabolism of organic acids in higher plants and microorganisms.

Boston University School of Medicine. I. Asimov. Radiation-induced changes in nucleic acids and their hydrolysis products.

The Children's Medical Center, Boston, Mass. S. Farber. Nature of bleeding in pancytopenia with special regard for thrombocytopenia and the vascular defect.

Emory University. H. W. Ades. Effect of radiation on learned behavior problem-solving ability and neural mechanism of Rhesus monkeys. Effect of radiation on ground substance of loose connective tissue.

Massachusetts General Hospital. J. C. Aub, I. T. Nathanson, and P. C. Zamecnik. Biochemical study of the effects of radiation on cells.

University of Michigan. F. J. Hodges and I. Lampe. Clinical evaluation of teletherapy.

New England Deaconess Hospital. S. P. Hicks *et al.* Acute and chronic radiation injury.

New York University-Bellevue Medical Center. J. M. Converse and M. Gaudino. Effect of refrigeration of human and animal skin upon its use in skin grafts in animals and man. Study of the antibodies produced by homologous skin grafts in animals and in man.

Philadelphia General Hospital. H. P. Schwarz. Effect of x-ray radiation on the infra-red spectra of neural and radiosensitive visceral tissue.

Western Reserve University. A. R. Moritz. Physiological and pathological aspects of thermal and flash burns.

University of Washington. F. I. Badgley. Atmospheric turbulence study.

The Radcliffe Graduate School of Arts and Sciences is inviting applications for the **Helen Putnam Fellowship for Advanced Research,** a postdoctoral resident fellowship for women. The recipient will be permitted to use research facilities at Harvard University. The research may be in any field related to human genetics or mental health, including psychology, child development, and other fields of social science. The stipend will be $3000 a year, with possibility of renewal. Application blanks may be obtained from the Secretary of the Graduate School, Radcliffe College, Cambridge 38, Mass. *Completed applications should be returned not later than April 1, 1954.*

The **University of Washington,** Department of Biochemistry, has announced the availability of several predoctoral fellowships for 1954–55. These offer stipends of $135 per month for the academic year, and remission of tuition and laboratory fees. Fellows are also eligible for full-time research assistantships during the summer that allow $270 monthly for three months. Applications should be addressed to the Executive Officer, Department of Biochemistry, University of Washington, Seattle 5.

In the Laboratories

The **Shell Chemical Corporation** has recently opened a $10,000,000 anhydrous ammonia plant in Ventura, Calif., that will have a productive capacity of 150 tons a day. Ammonia's most important application is as a fertilizer because it contains 82 percent nitrogen. The new plant will also produce ammonia for use in industry for refrigeration, and for the manufacture of synthetic fibres, explosives, pulp, and nitric acid.

All U.S. Department of the Navy studies of methods of protecting exposed surfaces of airplanes against corrosion, erosion, and ice coating are centered now at the **University of Cincinnati Applied Science Research Laboratory.** In addition to its own research in the field, the laboratory will be the official testing center for all materials considered by the Navy to have possibilities for use as plane coatings.

The **Westinghouse Electric Corporation** will build a new metals development plant at Blairsville, Pa. Scheduled for completion by late 1955, the plant, which is part of the company's $300,000,000 expansion program, will be devoted to metallurgical development and pilot production of special alloys and castings.

Construction has begun on a new $150,000 building to house the insecticide and animal laboratories of the **Wisconsin Alumni Research Foundation** (WARF) in Madison. The structure will stand immediately behind the present Foundation. It will house the insecticide testing division, which is expected to be about three times as large as the present division. The Foundation's tests for the insecticide industry involve screening numerous compounds for possible insecticidal activity and the conducting of control and development work. Projects with animals, including chick tests, warm blooded toxicity tests, and biological assays for vitamins, will be carried out. Completion of the building is planned for March, 1954.

Meetings and Elections

At the scientific award dinner of the mid-year meeting of the **American Pharmaceutical Manufacturers' Association,** the American-Korean Foundation cited the Association for its "overwhelming generosity in providing drugs, pharmaceuticals and medical supplies valued at over one million dollars to the people of Korea on the warm, voluntary 'Brother to Brother' basis that befits relationships between free peoples." The citation was signed by General James A. Van Fleet, chairman of the Foundation, and Milton S. Eisenhower, honorary chairman.

At the **23rd Annual Meeting of the American Association of Physics Teachers** to be held in New York City, Jan. 28–30, there will be sessions of contributed and invited papers and panel discussions. In the last category "The Responsibility of the Physics Teacher in Engineering Education" will be considered, with Dean L. E. Grinter of the University of Florida and Joseph H. Keenan of the Massachusetts Institute of Technology among the participants. There will also be a panel discussion of the important topic "Research Subsidies and College Teaching."

During a joint session with the **American Physical Society,** the retiring president of the Society will address the meeting; Enrico Fermi will speak on "What Can We Expect to Learn from High Energy Accelerators?"; and John A. Wheeler of Princeton University will deliver the 12th Richtmyer Memorial Lecture, "Fields and Particles."

The 4th annual meeting of the **Animal Care Panel** was held Dec. 2–3 at the University of Chicago. For the first time in its four-year history, the Panel met as an incorporated organization. Because the care of laboratory animals by specially trained professional personnel is a fairly new concept, until recently there has been little standardization in the field and an inadequate literature. As a result of the interest created by the new group, much has been accomplished both in improving specific areas of care, and in establishing higher standards for housing, nutrition, and sanitation.

The program for the meeting included reports on aspects of handling laboratory animals, such as nutrition of laboratory dogs, nutrition of small laboratory animals, and the selection of appropriate animal material for a given investigation. Other reports dealt with projects of particular timeliness. The Hormel Institute of Austin, Minn., contributed a paper on the development of miniature pigs for research purposes, pigs that weigh less than 70 pounds at maturity. Another paper discussed a colony of rats maintained germ-free, rodent-free, and parasite-free, at the Lobund Institute, Notre Dame.

Two reports of interest to research biologists were given. Orson N. Eaton, executive secretary of the newly formed Institute of Animal Resources, described the Institute's program; he also spoke on the development of the genetic concept of controlled pure animal strains. W. Lane-Petter of the Laboratory Animals Bureau outlined the conduct of animal experimentation in Great Britain. The British have long had licensing laws in effect that are of interest to American scientists in view of the current agitation in this country for adoption of similar legislation.

The Animal Care Panel publishes proceedings of each meeting and individual members of the Panel are available for consultation on problems relating to the care of laboratory animals. For further information about the Panel, or to obtain copies of the Proceedings, write to the secretary, Dr. R. J. Flynn, P.O. Box 299, Lemont, Ill.

Alfred C. Kinsey, professor of zoology at the Institute of Sex Research, Indiana University, will deliver the **29th Annual Hermann M. Biggs Memorial Lecture,** under the auspices of the Committee on Public Health Relations of The New York Academy of Medicine, on Feb. 4. His subject will be "Data on Female Sexual Behavior: Their Application in Clinical Medicine and Public Health." There will be three discussants: Sophia J. Kleegman, associate clinical professor of obstetrics and gynecology, New York University School of Medicine; Carney Landis, professor of psychology, Columbia University; and George Murdock, professor of anthropology, Yale University.

The **Association of Southeastern Biologists** will hold its 15th annual meeting April 15–17 at Louisiana State University, Baton Rouge. The Association is composed of more than 500 biologists from southern colleges, universities, and research institutions. President for 1954 is Bruce D. Reynolds of the University of Virginia. Mary E. Garlden of Oak Ridge, Tenn., is secretary. Also meeting with ASB will be the Southern Appalachian Botanical Club and the Southeastern Section, Botanical Society of America.

A special feature, a symposium on marine biology, will be held on the Thursday evening preceding the main sessions. Field trips will be arranged by the local committee at Baton Rouge. Cochairmen of this committee at Louisiana State University are George C. Kent, Department of Zoology, and H. E. Wheeler, Department of Botany.

The **3rd International Conference on Low Temperature Physics** held at The Rice Institute Dec. 17–22, 1953, was sponsored jointly by the National Science Foundation, the International Union of Pure and Applied Physics, and The Rice Institute. About 200 leading scientists in the field of low temperature physics from the United States and foreign nations met to discuss the latest research developments and theories dealing with temperatures approaching absolute zero.

Nine formal sessions were held during which papers were presented on research with liquid helium, magnetism under supercooled conditions, superconductivity, and solid state physics at low temperatures. Chairmen of the sessions were: J. F. Allen, St. Andrews University, Fife, Scotland; J. Bardeen, University of Illinois; H. Casimir, Phillips Company, Eindhoven, The Netherlands; K. Clusius, University of Zurich, Switzerland; P. Donzelot, French Science and Cultural Attaché, New York, N.Y.; A. Frolich, University of Liverpool, England; C. J. Gorter, University of Leiden, The Netherlands; L. C. Jackson, University of Bristol, England; P. Jacquinot, University of Paris, France; N. Kurti, University of Oxford, England; L. McKenzie, Interdepartmental Committee on Scientific Research and Development, Washington, D.C.; K. Mendelssohn, University of Oxford, England; W. Meissner, University of Munich, Germany; A. B. Pippard, Royal Society Mond Laboratory, Cambridge, Mass.; K. W. Taconis, University of Leiden, The Netherlands; A. van Itterbeek, University of Louvain, Belgium; L. Weil, Institut Fourier, Grenoble, France.

The conference was planned and directed by the following committee: W. V. Houston, The Rice Institute; C. T. Lane, Yale University; R. J. Seeger, National Science Foundation; J. Slater, Massachusetts Institute of Technology; C. F. Squire, The Rice Institute.

In conjunction with the annual meeting of the American Academy of Forensic Sciences, to take place in Chicago, Feb. 25–27, the Section on Pathology will hold a **Medico-Legal Slide Seminar** to be moderated by Arnold Strauss, pathologist to the Chief Medical Examiner's Office, Norfolk, Va. This seminar is designed to cover a wide range of problems frequently

encountered by forensic pathologists. The sets of slides and the protocols may be obtained by writing to Geoffrey T. Mann, Chairman, Section on Pathology, American Academy of Forensic Sciences, 404–406 N. 12 St., Richmond 19, Va. Each application must be accompanied by a check for $5 payable to Dr. Mann.

The **Professional Group on Electronic Component Parts** (PGECP) has been organized in the Institute of Radio Engineers for the purpose of promoting the continued improvement of electronic components and to provide channels for exchanging both functional and environmental test information on component parts among research, development, and production organizations. Floyd A. Paul of Northrop Aircraft, Inc. has been elected chairman of this group, whose field of interest includes the characteristics, limitations, applications, development, performance, and reliability of component parts.

This group—with the cooperation of the American Institute of Electrical Engineers, other professional groups of the IRE, the Radio-Electronics Television Manufacturers Association, and the West Coast Electronics Manufacturers Association, and with the active participation of the U.S. Department of Defense and the National Bureau of Standards—will sponsor the **Electronic Components Symposium** to be held in the Department of Interior in Washington on May 4–6. Speakers from both government and industrial organizations will take part in the symposium. Other activities planned by the group are the publication of a Transaction in the *Proceedings of the Institute of Radio Engineers* early in 1954, and the proposal of a scholarship plan to induce engineering electronic graduates to direct their activities toward the field of electronic component parts, and the creation of component part chapters in various cities throughout the country.

Membership in the PGECP is open to all IRE members, and interested engineers are urged to join. Application forms and detailed information may be obtained from Dr. Fred Haynes, Supervisor, Electronics Product Section, The Glenn L. Martin Co., Baltimore, Md., or application may be made directly to Miss Emily Sirjane, IRE, 1 East 79 St., New York 21, N.Y.

Miscellaneous

The following **chemicals** are wanted by the Registry of Rare Chemicals, Armour Research Foundation of Illinois Institute of Technology, 35 W. 33 St., Chicago 16: tellurium sulfide; bismuth telluride; ammonium cobalt thiocyanate; molybdenum oxyfluoride; ferrous oxide; butadiene monoxide; 8-hydroxy-1,2,3,4-tetrahydroquinoline; epifluorohydrin; 2,3-dihydrofuran; 1-amino-4,6,8-naphthalenetrisulfonic acid; N-methylvaline; 3,5-pyridinedicarboxylic acid; 2-pyrollecarboxylic acid; L-tropic acid; 1-decanesulfonic acid; glycolic aldehyde; sedoheptulose; L-ecgonine; D-isorhamnose; sinomenine.

A conference on heavy water reactors, organized by the Dutch-Norwegian Joint Establishment for Nuclear Energy Research, was held at Kjeller and Oslo on Aug. 11–13, 1953. The Proceedings of this conference, edited by J. A. Goedkoop and G. Jenssen, are now available as JENER Publication No. 7. The price per copy is 35,00 kr., postpaid. Checks should be made payable to The Joint Establishment for Nuclear Energy Research, Kjeller per Lillestrom, Norway.

In May the University of Hawaii Press is publishing Robert W. Hiatt's *Directory of Hydrobiological Laboratories and Personnel of North America.* This work lists 187 laboratories, and for each is included the address, senior officer, institutional affiliation, objectives, scope of activities, season of operation, and environments stressed. For the visiting investigator the volume will indicate the accommodations available, major research facilities, capital equipment, and provisions for publication; and for the prospective student, the instructional program, teaching facilities, and scientific staff. Biographical sketches of 1300 personnel are included, listing the institutional affiliation, mailing address, field of specialization, current research project, and field experience, by geographic regions.

During last summer, a group of persons interested in the establishment of a memorial at the Marine Biological Laboratory to the late **Edwin Grant Conklin** held an informal meeting at Woods Hole. As a result of this meeting a committee headed by William R. Amberson, University of Maryland School of Medicine, was constituted to seek funds and make plans for such a memorial.

Dr. Conklin's association with Woods Hole as an active research worker covered a span of 62 years—from 1890 to 1952. He became a member of the Corporation in 1894 and was a trustee from 1897 until the time of his death. Few have had a longer or more intimate connection with the Marine Biological Laboratory than he, and no one has been more devoted to its welfare.

It is hoped to secure a sum of at least $5000. A portion of this amount will be used to place a plaque in the main foyer of the M.B.L., similar to those now there in memory of other biologists who had a prominent part in the early development of the Laboratory. The remainder of the funds might be used to secure a portrait of Dr. Conklin, painted from life by Gertrude Whiting in 1946, or to provide in his memory a scholarship in the embryology course, or to establish a special annual lecture. Contributors to the fund are asked to transmit any suggestions they may wish to make regarding the type of memorial that should be established.

Contributions should be sent immediately to the treasurer, Mr. Homer P. Smith, Marine Biological Laboratory, Woods Hole, Mass. Contributors will be notified later concerning the amount raised and its disposition.

Technical Papers

Relationships of Fungi, Mites, and the Potato-rot Nematode[1]

A. D. Baker, Georgiana L. Brown, and Audrey B. James

Nematode Investigations Section, Entomology Laboratory, Ottawa, Canada

Frequent examinations of potato tubers infested with potato-rot nematode, *Ditylenchus destructor* Thorne, 1945 have disclosed a variety of conditions within the invaded areas, and in 1947 the senior author (*1*), reporting on experimental transfers, found that the progress of injury may vary widely between tubers even though they are all of the same variety from the same source and all inoculated on the same date with nematodes belonging to a common original population. Sometimes the destruction of potato tissue is rapid and may progress with little or no interruption until the greater part of the tuber is affected. In other cases, no appreciable injury to the tuber occurs even though live nematodes may be found near the point of inoculation 6 or 8 wk after their introduction. Several intermediate conditions have been noted. The possible relation of associated organisms, such as bacteria, fungi, mites, and other nematodes has been given attention. Wet rots (bacterial) appear to produce conditions unfavorable to the nematode. As a general rule, complete destruction of the potato tuber is not brought about by the nematodes, as a point seems to be reached where secondary, or associated, organisms complete the destruction. When this has occurred, it is difficult and usually impossible to locate any surviving nematodes; and, although it has been assumed that under natural conditions they return to the soil when the tuber breaks down, it now seems likely that at least the greater part of the population in a potato crop succumbs.

During many detailed examinations of infested potatoes it was observed that sometimes, where a large part of the tuber had been destroyed, there were very few nematodes in the bordering healthy potato tissue, and yet there were large populations in the areas that had been broken down. In such cases, fungus growth was abundant in the latter area. As it appeared likely that the nematodes were feeding on the fungus, both nematodes and fungi were transferred to Petri dishes containing potato dextrose agar, and the nematodes were propagated in this way. These results were confirmed later by repeated successful inoculations of fungus plates with the potato-rot nematode.

Nematodes in these fungus plates tend to assemble in and around the fungus colonies, and they have been frequently observed feeding on the mycelium. It is now evident that live potato tissue is not essential for the propagation of these nematodes, and transfers to potato agar without the fungus colonies were invariably unsuccessful.

In 1951 Seinhorst and Bels (*2*) reported *Ditylenchus destructor* as attacking mushrooms, and Cairns (*3*) has more recently reported *Ditylenchus* sp. feeding on this host in the United States. The fungus cultures that the potato-rot nematode will feed on may include many species. Host fungi already identified at the Ottawa laboratory include three species of *Fusarium,* a species of *Mucor,* possibly *M. hiemalis* Wehmer, and *Trichoderma viride* Pers. ex. Fr.[2] On observing these nematodes with their stylets inserted in a fine strand of mycelium considerably less than their own diameter, one wonders how much nourishment can be obtained from each puncture. However, with fungi having nonseptate mycelium, the efficiency of the operation becomes more understandable.

Mites have been frequently found in association with nematode-infested tubers. It has also been observed that when the mite populations were large the nematode populations declined sharply. In the culturing of these nematodes on fungus plates, the mites fed on the fungi, and they can injure a fungus colony very quickly. If the fungus is largely consumed the nematodes disappear, and it is now indicated that this is what may take place frequently in potato tubers.

In an earlier paper (*2*) the "feeding front" of these nematodes within potato tubers was referred to. It is behind this feeding front that a "fungus garden" is built up in the tuber, and one may speculate that the main activity of the nematodes is in building up this garden rather than in direct feeding on live potato tissue. When this fungus garden has been well established, most of the nematodes are found in this area. There is at least some indication that fungus colonies may be necessary for the most successful development of these nematodes in the potato. If mites gain entrance to a nematode-infested tuber the fungus garden is often destroyed and the nematodes disappear. A species of mite that attacks these fungi is *Tyrophagus putrescentiae* (Schr.); another species, *Histiostoma feroniarum* (Dief.), has been identified.[3]

To solve the species problem that may be involved in these potato-rot nematode populations, many attempts have been made to build up pure colonies of the nematodes through single-female transfers to potato tubers. That this could be done was first demonstrated here in 1947. Greater attention has been recently given to this method. A number of these single-female colonies have been established but only after a very large number of attempted transfers. With the development of our technic for rearing these nematodes on fungus cultures, the single-female colonies were transferred to fungus cultures, with the idea that

[1] Contribution No. 3114, Entomology Division, Science Service, Department of Agriculture, Ottawa, Canada.

[2] Through the kindness of J. W. Groves, Botany and Plant Pathology Division, Ottawa, Canada.

[3] Through the courtesy of H. H. J. Nesbitt, Carleton College, Ottawa, Canada.

by this means they could be more rapidly built up and maintained. In most cases these transfers have been very successful, only a few of the colonies have succumbed. The failures may have been due to the normal hazards accompanying transfers, but the possibility is recognized that a species complex may exist in the potato populations. It is possible that intimate relationships between plant-parasitic nematodes and fungi may prove to be more common and important than has been hitherto suspected.

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The Separation of Neuroblasts and Other Cells from Grasshopper Embryos[1]

Georgia S. St. Amand and Samuel R. Tipton

Biology Division, Oak Ridge National Laboratory, Oak Ridge, and University of Tennessee, Knoxville

In the course of our studies of the effects of x-rays on the metabolism of grasshopper embryos (*Chortophaga viridifasciata* DeGeer), it was desirable to have suspensions of free cells in as near normal morphological and physiological condition as possible. Adequate suspensions have been obtained through enzymatic digestion of the intercellular substance. Neuroblasts as well as other types of embryonic cells from these suspensions undergo mitosis and maintain active respiration for several hours after separation. The method developed, somewhat similar to the method of separation of chick embryo cell suspensions described by Moscona (*1*), utilizes a digestive mixture of trypsin and hyaluronidase in a calcium-free medium at pH 7.4. Trypsin was essential for adequate solution of the intercellular substance, whereas the development of gel in the medium was lessened considerably by the addition of hyaluronidase. It is well known that calcium-free media decrease the adhesiveness of embryonic cells (*2, 3*) and cells of mature invertebrate and vertebrate tissues (*4–7*).

Routinely, 150 embryos (average total dry weight, 5.25 mg), selected morphologically at a stage equivalent to that of 14 days development at 26° C, were removed from the eggs under aseptic conditions in an isotonic salt medium containing calcium. After rinsing twice in a calcium-free medium to remove residual calcium, yolk, and egg fluid, the embryos are placed in 5 ml of digestive mixture for 1 hr at 38° C. The digestion mixture consisted of 7.5 mg each of recrystallized trypsin (Worthington) and bovine testis hyaluronidase (Armour or Mann) in 10 ml of calcium-free solution. Agitation during the period of digestion was avoided as this resulted in very viscous solutions, or gel formation, and clumping of the embryos. At the end of the hour 0.5 ml of protein solution (5 mg of Armour bovine albumin/0.5 ml calcium-free medium) was added to the digest suspension. Holter and Zeuthen (*8*) used egg white to decrease the adhesiveness of ascidian eggs to glass or to one another, and in our experience the albumin aided in overcoming stickiness among separated cells. At this stage the general form of the embryos was still distinguishable. Individual cells were separated by forcing embryos and solution slowly into and out of a small pipet with a rather large bore. Separation must be done carefully and gently for mechanical damage results in "bleb" formation at the cell surface, and few or no dividing cells can subsequently be observed in the suspension. When the solution is quite milky and all large particles have been broken up, it is transferred to a centrifuge tube with 5 ml of culture-medium containing calcium. After centrifugation at 158 rpm on a clinical centrifuge for 15 min (distance from axis to bottom of tube, 21 cm), the residue was resuspended in 0.6 ml of fresh medium. Cell separation was fairly complete, and no evidence of reaggregation of separated cells has been obtained. Hemocytometer counts of a typical suspension gave 2,000,000 cells, or about 13,300 cells/embryo, a figure which is undoubtedly low because of the unavoidable loss of cells during separation.

In Fig. 1 is shown the endogenous oxygen consumption of a cell suspension containing 1,732,000 cells measured at 38° C, in an atmosphere of oxygen. Respiration decreases after 3 hr, possibly due to lack of substrate. The average rate of oxygen consumption of the suspension shown in Fig. 1 was 12.7 mm^3 of oxygen/hr at 38° C. In Warburg determinations of the respiration of intact embryos, we have obtained an average value of 31.5 mm^3 of oxygen/hr for 150 embryos. The difference between these two values, 31.5 and 12.7, may be a measure of the yield of embryonic cells in the suspension, but with the evidence at hand

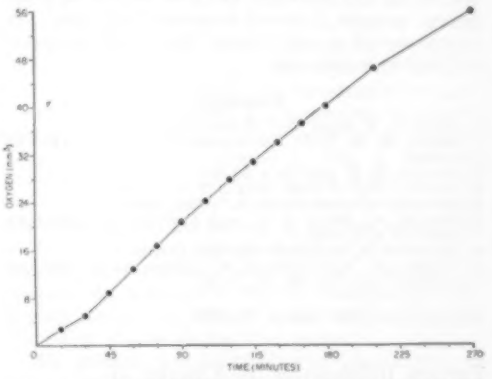

Fig. 1. The endogenous respiration of a grasshopper embryonic cell suspension in isotonic salt solution.

[1] Work performed under contract No. W-7405-eng-26 for the Atomic Energy Commission.

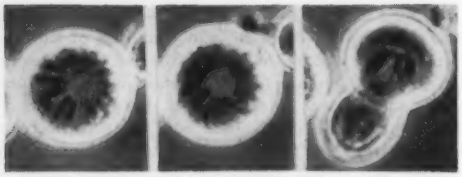

FIG. 2. Three views of a neuroblast cell in anaphase in a typical embryonic cell suspension prepared from a trypsin-hyaluronidase digest in calcium-free salt solution. Rotation of the cell has occurred so that two of the photomicrographs are polar views and the third is a side view. Neuroblasts normally divide unequally: the smaller daughter cell is the ganglion cell. Other cell types in the suspension divide equally.

it is not possible to determine whether the low value of cell respiration in the suspension is due to loss of cells in the separation, or to a decreased rate of respiration per cell.

For 7–8 hr after separation, dividing cells can be seen in suspension (Fig. 2). Detailed observations on division have been limited to mid-mitotic phases, and these phases proceed as in the intact embryo, but cursory examination of other phases has revealed no deviation from the normal. Second divisions of neuroblasts in the suspension have been observed.

It should be feasible to isolate neuroblasts or other types of embryonic cells from such a suspension for particular cytological or physiological study. Although the use of this technique has been limited to grasshopper embryos, it should be adaptable to other embryonic as well as adult tissues where a cell suspension or isolation is desirable.

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Factors Influencing the Uptake of Iron by Blood and by Bone Marrow Cells *in Vitro*

Gordon H. Ellis,[1] C. Stafford Brandt, and E. J. Thacker

U.S. Plant, Soil, and Nutrition Laboratory, Bureau of Plant Industry, Soils, and Agricultural Engineering, A.R.A., U.S. Department of Agriculture, Ithaca, New York

To investigate the mode of action of copper in iron metabolism, the technique used by Walsh *et al.* (*1*) to determine iron uptake by cells was used. The iron used was a mixture of Fe^{55} and Fe^{59} [2] and had a specific activity of approximately 2 mc/g Fe. It was added to the culture medium as ferrous ammonium sulfate. The blood cells were obtained from rabbits that were bled repeatedly to increase the reticulocyte count. The bone marrow cells were obtained from chicks or turkey poults.

The amount of iron uptake is dependent upon the washing of the cells in 0.93% NaCl prior to incubation. One milliliter of heparinized blood (reticulocyte count 6%, hemoglobin 9.5%) gave a count of 150 cpm after 8 hr of incubation. When washed once in 3 volumes of saline, before incubation, a count of 640 cpm was obtained. The 100 μg of Fe used gave a count of 25,700 cpm. In another experiment (11.7% reticulocytes) the cells were washed one, two, and three times and counts of 540, 900, and 930 cpm, respectively, were found. The influence of copper, the number of cells, and the iron level are shown by the data in Table 1.

TABLE 1.

Number of cells (washed once)	100 μg Fe 9 μg Cu (cpm)	100 μg Fe (cpm)	50 μg Fe (cpm)
1.63×10^6	1770	460	440
3.26×10^6	950	650	460
6.52×10^6	880	620	610

The addition of copper increases the iron uptake, particularly with fewer cells. Reducing the amount of iron has little effect. Where copper is present, fewer cells take up more iron than do larger numbers. In another trial, halving the iron approximately halved the uptake.

Similar results were found with bone marrow cells. These were obtained by crushing the long bones in isotonic saline, filtering through glass wool to remove extraneous material, and further isolation by slow centrifugation, following the technique of Magnussen (*2*). When resuspended in saline and again centrifuged, the washed cells took up 2.4 times more iron than those not washed. A second washing caused no further uptake. The effect of iron and copper levels is shown in Table 2.

It can be seen that as the level of iron supply is increased, the amount of iron uptake is increased. In-

TABLE 2.

μg Fe added	μg Cu added as the acetate (cpm)			
	0	5.7	11.4	22.8
10	270	350	440	870
40	1300	1800	1800	3000
120	4700	7400	7400	8300
120	3(0)*			200*

* Incubated 20 min; others, 6 hr. Total cells/culture tube 1.25×10^6: 100 μg Fe gives 12,700 cpm. Each datum is the average of 2 runs. Cells were from 5- to 6-wk-old chicks.

[1] Present address: Wyeth Institute for Applied Biochemical Research, Philadelphia.

[2] From the isotope division of AEC at Oak Ridge.

creasing the copper supply does the same, particularly at the lower level of iron. The uptake of iron is greatly reduced as the time of incubation is shortened.

Walsh *et al.* (*1*) reported a correlation between reticulocyte count and iron uptake when using blood from pernicious anemia patients in remission, and concluded that their results could be interpreted in physiologic terms. In our studies with rabbit blood this correlation was not obtained. The iron uptake by blood cells was considerable and was increased by the inclusion of copper in the culture medium. As the amount was influenced by several other factors and was far in excess of that which could possibly be used in hemoglobin synthesis, this result is not interpreted in physiologic terms. Our results indicate that the mechanism which determines iron uptake must be fairly complex.

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Radioactive Gold in Filter Paper Electrophoresis Patterns of Plasma

Norman Simon[1]

Departments of Physics and Radiotherapy of the Mount Sinai Hospital, New York

When radioactive colloidal gold is injected into the pleural or peritoneal cavities of patients with effusions, small but measurable amounts of radioactivity circulate in the blood. Andrews *et al.* (*1*) have indicated that less than 1% of the given dose is in the blood at one time. This finding was confirmed in a series of patients treated at the Mount Sinai Hospital (*2*). Less than 0.2% of the given dose in the serous cavity was encountered in the circulating blood.

The gold in the blood is in the plasma; the red blood cells and white blood cells contain no measurable radioactivity. When trichloracetic acid is added to plasma the gold is in the protein precipitate. To determine whether gold in plasma is coprecipitated with or bound to protein presents a problem. If the gold is bound to protein it is of further interest to know which protein fractions bind the gold.

Attempts to solve these problems by using chemical methods of protein separation have yielded inaccurate results. Separating the proteins by electrophoresis would be a cumbersome procedure. Filter paper electrophoresis, however, is a method that simplifies the separation of plasma proteins (*3*) and lends itself to the determination of which protein fractions bind radioactive gold (*4*). In this method a current is passed through a strip of filter paper which has been soaked in buffer solution. The ends of the filter paper dip into positive and negative electrode vessels. Samples of protein-containing solution are applied to the paper, and proteins migrate with the current. Separation of the protein fractions is satisfactory in a few hours. These fractions can be dyed differentially for identification.

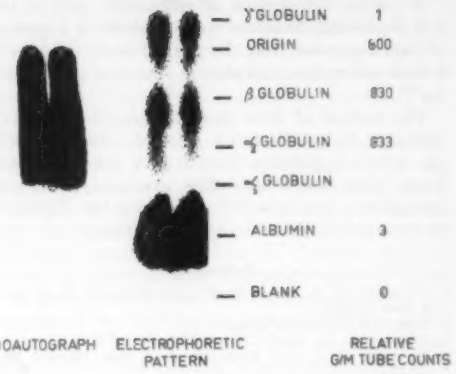

Fig. 1.

Radioactive colloidal gold (Au^{198}) was added to normal plasma *in vitro* (500 μc Au^{198} to 200 cc plasma), and samples of this solution were precipitated with trichloracetic acid at time intervals following the mixture of these two components. Counting the radioactivity of these precipitated samples showed that the uptake of radioactive gold in the proteins was maximal within 15 min. The proteins in the original solution containing gold (before precipitation) were then separated by applying about .030 cc of the plasma to filter paper. Figure 1 shows the filter paper electrophoretic pattern of these separated proteins and identifies the fractions. The distribution of radioactive gold in this pattern was determined by Geiger-Muller tube counts of various areas in the electrophoretic pattern as indicated in Fig. 1. The thin window (5 mg/cm²) of the tube was 6 mm in diameter. A radioautograph of the same electrophoretic pattern confirmed the binding of radioactive colloidal gold to the α and β globulin fractions of the plasma proteins; no gold was bound to the γ globulin or albumin. As indicated in Fig. 1, considerable radioactivity remained at the site of the originally applied droplet of plasma on the filter paper.

This process was repeated with plasma from a patient who had received an intrapleural injection of 60 mc of Au^{198} 24 hr previously. The distribution of Au^{198} in the plasma protein in this patient is similar to the distribution in the plasma to which gold had been added *in vitro*.

In the filter paper electrophoretic pattern of ascitic fluid from a patient who had carcinoma of the pancreas, the ascitic fluid was aspirated from the peritoneal cavity one day after the intraperitoneal injection of 142 mc of Au^{198}. The gold is distributed in essentially the same fractions as in the blood. Some of the gold is unfixed to the globulin and remains at the point of application (origin) of the ascitic fluid on the filter paper.

[1] The author acknowledges the cooperation of Arthur W. Ludwig in this work.

A similar distribution of radioactive gold in the α and β globulin fractions was obtained in a specimen of fluid aspirated from the pleural cavity of a patient 6 days after the intrapleural injection of 56 mc of Au^{198}.

The method of filter paper electrophoresis has established that radioactive colloidal gold is bound to the α and β globulin fractions of plasma proteins. Even more important, this previously introduced method is a simple tool for studying the distribution of radioactivity in blood and its proteins.

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The Multiple Etiology of Obesity: Production of Two Types of Obesity in Littermate Mice[1]

J. Mayer and C. Y. Zighera

Department of Nutrition, Harvard School of Public Health, Boston, Massachusetts

A number of types of experimental obesity have been studied in this and other laboratories (*1*): hypothalamic obesity in the rat, yellow obesity (dominant) in the mouse, the hereditary (Mendelian recessive) obese-hyperglycemic syndrome,[2] thalamic obesity in the monkey, hereditary (Mendelian recessive) obesity in the Shetland sheep dog, immobilization obesity in the rat, and goldthioglucose obesity in the mouse. Unfortunately, these obesities have usually been produced in different animal species or at least in different strains, and their metabolic similarities and differences have rarely been studied simultaneously. We wish to report here, first a comparison between two types of obesity in different strains of mice, and next the establishment of these two types in littermate animals with direct comparison of metabolic characteristics.

The hereditary obese hyperglycemic syndrome is characterized in particular by extreme overweight (limit weights of 50–115 g as compared to 25–30 g) and by a form of hyperglycemia sensitive to diet and to growth hormone and extremely resistant to large doses of insulin (*2*). Recent evidence (*3*) indicates that these animals are characterized by oversecretion of a hormone secreted by the alpha cells of the islets of Langerhans, of which growth hormone is the tropic hormone.

Goldthioglucose obesity (*4*) is produced by injection of the LD_{50} dose of goldthioglucose. About 30% of the animals that survive injection become obese, the limiting weight is in the 50–95 g range. No metabolic study has been conducted in these animals.

The blood glucose levels, effect of insulin, and effect of growth hormone were determined in 3 groups of Swiss mice: goldthioglucose-treated obese animals (range 40–54 g), goldthioglucose-treated nonobese animals (range 20–24 g), and untreated controls (range 20–28 g). These animals had been injected 8 mo previously with 15 mg of goldthioglucose.[3] The same procedure was conducted simultaneously in 3 groups of animals of the genetically obese stock, obese (80–115 and 40–55 g), and nonobese (18–27 g) mice representing age and weight controls, and described in Table 1, and 1 group of nonobese littermates of young hereditarily obese animals, made obese (40–56 g) by goldthioglucose injection. This last group represented the obese survivors of 5 equal groups of 20 animals injected with 15, 25, 35, 40, and 50 g of goldthioglucose. None of the animals injected with 15 or 25 mg had developed obesity; all animals injected with 50 mg died. Eight of the 20 animals injected with 35 mg and 9 of the 20 animals injected with 40 mg died. Three animals injected with 35 mg and 9 animals

Table 1. Effect of growth hormone on blood glucose in goldthioglucose obesity and in the hereditary obese hyperglycemic syndrome.

Animals			Blood glucose (mg %)	
Type	Number	Weight (g)[4]	Untreated	After growth hormone
Goldthioglucose treated, obese Swiss	12	45.3 ± 4	118 ± 9	110 ± 14
Goldthioglucose treated, nonobese Swiss	12	22.8 ± 0.7	107 ± 11	105 ± 6
Untreated Swiss	12	24.0 ± 2	105 ± 7	97 ± 6
Hereditary obese-hyperglycemic, 3½ mo old (weight controls)	8	45.2 ± 3	160 ± 20	303 ± 4
Hereditary obese-hyperglycemic 9 mo old (age controls)	8	92.0 ± 11	298 ± 41	485 ± 82
Nonobese *ob ob* littermates	12	23.8 ± 4	115 ± 7	116 ± 16
Nonobese *ob ob* littermates made obese by goldthioglucose	8	45.2 ± 5	124 ± 15	106 ± 12

[1] Supported in part by grants-in-aid from the National Institute of Arthritis and Metabolic Diseases and the National Heart Institute, National Institutes of Health, U.S. Public Health Service, Bethesda, Md., and the Nutrition Foundation, Inc., New York City.

[2] The term hyperglycemia, which represents a condition either found naturally in the obese animals or immediately elicited by small doses of growth hormone to which the nonobese animals are insensitive (*3*) is much to be prefered to the term "diabetes" previously used. If by diabetes is meant the insulin-free condition, the obese animals are not diabetic.

[3] Supplied by Schering Corp., Bloomfield, N. J. These animals were given by G. Brecher, National Institute of Arthritis and Metabolic Diseases, Bethesda, Md.

injected with 40 mg developed, in 2–3 mo, weights exceeding 40 g.

Blood glucose levels before and after growth hormone treatment are given in Table 1. The dosage used was 2 mg/day for 3 consecutive days before the determination. It is readily seen that goldthioglucose obese animals do not show hyperglycemia as do the hereditarily obese hyperglycemic animals. The fact that this difference does not simply reflect strain idiosyncracies is demonstrated by the fact that the littermates of *ob ob* mice[4] made obese by goldthioglucose show blood glucose levels in the normal range. Similarly, goldthioglucose obese animals, whether Swiss or littermates of *ob ob* mice, do not exhibit any increase in blood glucose when treated with growth hormone, as do mice with the hereditary obese-hyperglycemic syndrome. In the latter, the response is so quantifiable that it has been made the basis of a method of determination (*5*).

Finally, it was found that subcutaneous injection of one unit of insulin was enough to cause hypoglycemic convulsions in all groups of Swiss mice (including the goldthioglucose obese animals), in nonobese littermates of *ob ob* mice, and in littermates of *ob ob* mice made obese by goldthioglucose treatment. By contrast, as reported previously (*2*), the blood glucose of animals with the obese hyperglycemic syndrome is totally unaffected by one unit of insulin, hardly affected by 20 units of insulin, and the animals can survive injection of even larger doses.

The profound metabolic difference between the two types of obesity is all the more striking in that the siblings, whether genetically obese or chemically obese, are completely identical in external appearance. Although fat deposition in all cases is dependent on positive caloric balance, these findings illustrate the fact that the existence of such a positive balance is not per se an explanation of obesity. It is simply a restatement of the first law of thermodynamics. In all cases, the real problem is to find the primary causes of this relative hyperphagia. Obesity appears to be a common end-result of syndromes of profoundly diversified etiologies (*1*).

[4] By *ob ob* mice is meant the animals in which the hereditary syndrome is present.

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Experiences with Transplantation of the Lung

Creighton A. Hardin and C. Frederick Kittle[1]

The Department of Surgery,
University of Kansas Medical Center, Kansas City

Relatively few studies pertinent to the transplantation of lung tissue have been made. Several workers have described (*1–3*) various types of autogenous and homologous lung transplants and have demonstrated the technical feasibility of such procedures.

Our initial experiences (*4*) were concerned with transplantation of the entire left lung from one dog to another. The left lung was removed from a donor animal by transecting the left auricle, the left main pulmonary artery, and the left bronchus. Left pneumonectomy was then done in the recipient animal. The donor lung was grafted to the recipient animal by anastomosing the left auricle, the left main pulmonary artery, and the main stem bronchus. Following these anastomoses, the grafted lung expanded, blood flowed throughout it, and to all gross inspection it appeared normal.

In a control group of 10 such homologous lung grafts the animals survived from 1 to 12 days with death usually resulting from pneumonia. Microscopic examination of the transplanted lung tissue at autopsy suggested that the changes were due to tissue incompatibility. In another group of 3 dogs wherein the donor and recipient animals were littermates, the survival period ranged from 13 to 30 days, significantly longer than the control group. In an attempt to alter the systemic antigen-antibody response, other groups of 3 dogs each were given benadryl (150 to 200 mg daily), cortisone (35 to 45 mg daily), or total body radiation (400 r) during their immediate postoperative course. Those animals receiving benadryl or total body radiation showed no appreciable difference in survival from the control dogs. Those to which cortisone was administered survived longer, from 12 to 18 days.

Subsequently we became interested in the role of the spleen and its possible effect in the viability of lung transplants. That splenectomy may reduce an animal's ability to produce antibodies has previously been demonstrated (*5*). In a group of 5 dogs splenectomy was done concomitantly with homologous left lung transplant. In another group of 6 dogs (the re-

[1] Markle Scholar in Medical Sciences.

Table 1. Survival in homologous lung transplants.

Group	Number of dogs	Days of survival
Control	10	1, 2, 2, 3, 3, 4, 7, 11, 11, 12
Donor and recipient littermates	3	13, 20, 30
Benadryl	3	5, 6, 6
Cortisone	3	4, 12, 14
Radiation	3	4, 7, 8
Splenectomy at time of transplant	5	2, 4, 7, 7, 8
Splenectomy preceding transplant	6	2, 5, 5, 7, 8, 9

cipient animals) splenectomy was done 11 to 16 days prior to the left lung transplant. In neither group was the survival time enhanced by splenectomy.

That an animal survives or expires following homologous lung transplantation is not proof of the viability, necrosis, or functional ability of the transplanted lung. To elucidate this further, homologous left lung transplantation was done in 5 dogs which were then immediately subjected to right pneumonectomy. In 3 animals death occurred either during the operation or within 25 minutes after its completion. However, the remaining 2 animals survived for 6 and 9 days, proving unequivocally the functional ability of the homologous lung during these periods.

Although the operative technique of transplantation of one entire lung has been demonstrated to be feasible, the limitations imposed by foreign protein implantation appear responsible for the present failure of these organs to survive. Further studies are in progress to investigate the antigen-antibody mechanism in these homologous lung transplants and possible methods of altering it. The survival of quick-frozen lung grafts after transplantation is being considered.

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A Comparison of the Total Protein and Albumin Content of the Blood Sera of Some Reptiles[1]

Elias Cohen[2, 3]

Department of Zoology,
Rutgers University, New Brunswick, New Jersey

Precipitin studies in the systematic serology of vertebrates are usually carried out with native sera as antigens. DeFalco (*1*) in a study of avian relationships, suggested that some discrepancies in the percentage relationships obtained might have been due to differences in albumin/globulin ratios of the serum antigens. Haurowitz (*2*) has stated that one cannot generalize about proportions of serum albumins and globulins on the basis of human A/G ratios.

Deutsch and Goodloe (*3*), in an electrophoretic survey of plasma from 20 species of animals, found species differences in mobility, amount, and number of protein components. Notwithstanding, the analytical data were relatively constant in a given species. Fowl, in particular, had larger amounts of protein with low mobility components (possibly globulins) than did the mammals.

Deutsch and McShan (*4*) later studied the blood serum proteins of lower animals. Reptiles and amphibians have a greater proportion of low mobility serum protein components (globulins) than do normal higher vertebrates. Deutsch and McShan called the electrophoresis patterns of snake sera "unique." Species specificity was shown by the fact that diamond-back and timber rattlesnake patterns are easily distinguishable. Gleason and Friedberg (*5*) also detected a preponderance of low mobility components in the serum of a turtle.

In the present study, the total protein content and the albumin fraction of the native blood sera of a number of snakes and turtles were determined by the biuret method of Gornall *et al.* (*6*), the results were spot-checked against Kjeldahl analysis. Blood specimens were collected from the snakes by decapitation, whereas cardiac puncture was effective in obtaining blood from the turtles. Sera were obtained by standard serological procedures and became the property of the Serological Museum of Rutgers University. Data collected during this study are presented in Tables 1 and 2.

Statistical analysis of the data[4] revealed that for

Table 1. Snake serum proteins (g/100 ml of serum).

Species	Total protein	Albumin
Crotalus r. ruber (1)*	5.80	2.60
C. adamanteus (1)	2.75	0.11
C. v. viridis (7)	2.79	1.57
C. v. oreganus (1)	3.86	1.88
C. h. horridus (3)	2.50	1.08
Agkistrodon piscivorus (4)	4.52	1.20
Naja n. naja (1)	4.28	2.34
Lapemis curtus (1)	2.88	1.40
Natrix s. sipedon (1)	4.65	2.00
Lampropeltis getulus californiae (1)	4.10	2.20
Pituophis c. catenifer (1)	5.35	3.53
Coluber c. constrictor (1)	5.65	3.00
Thamnophis s. sirtalis (1)	3.20	1.80

* Number of specimens used shown in parentheses.

Table 2. Turtle serum proteins (g/100 ml of serum).

Species	Total protein	Albumin
Chelydra serpentina (1)*	5.00	1.60
C. serpentina (1)	2.60	0.65
C. serpentina (1)	5.04	0.90
Chrysemys elegans (1)	2.43	0.50
Clemmys marmorata (1)	3.20	1.40
Testudo spp. (Aldabra) (1)	2.74	0.50
Dermochelys coriacea (1)	3.70	1.42
Caretta caretta (1)	2.22	0.65

* Number of specimens used shown in parentheses.

[1] Section of a thesis accepted as partially fulfilling the requirements for the Ph.D., Rutgers University, New Brunswick, N. J.

[2] Present address: Department of Pathology, University of Oklahoma School of Medicine, Oklahoma City.

[3] The writer wishes to express his sincere thanks to all those who provided the sera or live specimens for this study.

[4] C. R. Doering, Department of Preventive Medicine and Public Health, University of Oklahoma, School of Medicine, is responsible for the statistical treatment of the data.

total protein content, the snake and turtle sera do not differ in their means or in their variation. However, for albumin content they do differ significantly.

The albumin values obtained in this study compare favorably with the electrophoresis data of Deutsch and McShan, who found that turtle sera contain more low mobility components (suggestive of globulins) than do snake sera. In fact, the albumin proportions of the majority of the snake sera were twice those of the turtles.

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The Effect of Serum Ultrafiltrate on Cultivated Mast Cells and Fibroblasts from Human Skin[1]

Elsa M. Zitcer and Paul L. Kirk[2]

Department of Biochemistry,
University of California, Berkeley

In a previous study of the cultivation of human tissue mast cells undertaken in this laboratory (*1*), serum ultrafiltrate was shown to stimulate cytoplasmic granulation when used as a constituent of the medium (chick embryonic extract, with or without cord serum). At the same time it was found that in the presence of cord serum the ultrafiltrate promoted proliferation, whereas in the absence of cord serum it inhibited proliferation, caused marked differentiation, and led to the death of the cells. Since fibroblasts from normal human skin were not cultivated as controls during the previous investigation, the significance of the effect of serum ultrafiltrate could not be evaluated. The present paper reports the results of a 6-month comparative study of the effect of serum ultrafiltrate on cultivated mast cells and fibroblasts, both of human origin.

Following the procedure employed in the earlier work, identical Carrel-flask cultures were prepared from a skin-lesion biopsy of an infant with urticaria pigmentosa and a biopsy of normal human adult skin. Supravital staining with toluidine blue confirmed the identity of the cells in the original cultures from the urticaria pigmentosa tissue, and in subsequent subcultures, by producing metachromasia, the accepted criterion for mast cells. No metachromasia was noted in the normal skin cultures, or in subsequent subcultures, when these were stained in the same manner. Three test media were used: (1) 40% serum ultrafiltrate, (2) 40% cord serum, and (3) 20% serum ultrafiltrate and 20% cord serum. The balance of each medium consisted of 4% embryonic extract and 56% Tyrode's solution.

The fibroblasts from the normal skin cultures grew, as described by Gey and Gey (*2*), in a dense radial network in all media, and mitosis occurred frequently. Some fine cytoplasmic granulation was noted in cultures maintained on medium 2. In cultures using media 1 and 3, the cytoplasm remained free of any granulation. This is consistent with the findings of Simms and Stillman (*3*) in their studies of the effect of serum ultrafiltrate. Growth was sufficiently rapid to permit subculturing every 3 or 4 wk.

The mast cells responded differently to each of the three test media. In cultures maintained on medium 1 the growth was sparse, and the large spindle-shaped cells divided only by amitosis. Differentiation was noted during the first week. The cells formed thickened stalks, and the cytoplasm was densely packed with coarse granules. After 2 wk no further proliferation occurred, and the cells became rounded; at 3 wk they were dead. Media 2 and 3 stimulated excellent growth, and the cells formed a dense radial pattern. Both mitotic and amitotic divisions were noted in these cultures. The cells were of great size, with large regular nuclei, often containing two or more nucleoli. Proliferation was slower than in the fibroblast cultures. It took 6–7 wk to attain adequate outgrowth for subculturing. In cultures placed on medium 2 the cytoplasmic granules varied greatly in size and number, although granulation, in general, was sparse. In cultures using medium 3, however, the cytoplasmic granules were uniformly coarse and so profuse that in some cases they obscured the nuclei. All the above results are in agreement with our previous study.

When fragments of the two tissue strains were grown side by side in the same Carrel flask with medium 3, no alteration of their individual characteristics was observed. Serum ultrafiltrate appears to have a differential effect upon the cytoplasmic granulation in the cells from the two tissue strains used in this study. The fibroblasts remained free of any cytoplasmic granulation, whereas cytoplasmic granulation in the mast cells was uniformly stimulated.

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[2] The authors express their gratitude to Dr. Rachel Reed, Pathology Department, Naval Radiological Defense Laboratory, San Francisco, for the urticaria pigmentosa tissue and for valuable consultation; to Dr. Harry Aitken, Berkeley, for the biopsy of normal human adult skin; and to Dr. Josephine Borson, Berkeley, for the cord blood.

Comments and Communications

Method for Obtaining Venous Blood from the Orbital Sinus of the Rat or Mouse

BLEEDING by cardiac puncture has been a frustrating problem to those working with rats in experiments requiring considerable quantities of blood. Death of the animal from shock is too frequent, and investigators must be prepared for decimation of their animal population over any extended period of time.

This note is prompted by the enthusiastic reception given our demonstration of a simple method, originated by B. N. Halpern of the Hôpital Broussais in Paris, France. This permits frequent bleeding without serious effects on the animal. Over 1 ml of venous blood can consistently be obtained from the orbital sinus of the rat.

A glass tubing, 6–8 in. in length and 4–6 mm in diameter, drawn out to pipet form is again drawn to provide a capillary puncturing end about 1 in. long. The bore of the puncture end should easily permit the free flow of blood. The animal is held immobile on its side against a table top by a firm grip, permitting the head to be pressed down with the thumb and forefinger. The capillary end of the glass tubing is introduced into the orbit of the eye at the anterior angle formed by the lids and the nictitating membrane. A short thrust past the eyeball will enter the slightly resistant thorny membrane of the sinus. The eyeball itself remains uninjured. As soon as the sinus is punctured, blood enters the tubing by its own pressure.

The tube can be sealed and the blood centrifuged without transfer. Heparinization of the tubes permits the taking of larger samples. Stress on the animal can be further reduced by 2 drops of 2% cocaine administered topically before bleeding. We have used this method, applicable also to the mouse, upon hundreds of rats without fatality.

SANFORD H. STONE

Pediatrics Research Laboratory
New York Medical College

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On the Histochemical Localization of the Mercurial Inhibition of Succinic Dehydrogenase in Rat Kidney

IN a recent communication, Mustakallio and Telkka (*1*) stated that after the administration of mercurial diuretics to the rat, succinic dehydrogenase first disappeared from the ascending portions of Henle's loops. Since this observation, if confirmed, would represent the first direct microscopic proof for an action of mercurial diuretics on distal segments of the tubular system, we wish to communicate our own findings.

In a report dealing with the influence of experimental kidney damage on histochemically demonstrable succinic dehydrogenase activity in the rat, we also studied the influence of a mercurial diuretic (*2*). We injected Meralluride Sodium[1] (mercuhydrin sodium) in amounts of 10 mg Hg/kg of weight. This amount will produce regularly renal necrosis (*3*) which apparently is localized, as with mercury bichloride, within the terminal portions of the proximal convolutions (*4*). We found, as with other kidney damaging agents, e.g., *dl*-serine, reduction of the histochemically demonstrable succinic dehydrogenase 45–60 min after the subcutaneous injection of the drug within the damaged cells of the proximal convoluted tubules. The thick loops of Henle which can be easily recognized by their intense staining reaction, however, retained their enzymatic activity. The same results were obtained when even larger doses of up to 40 mg Hg/kg of weight were used, as suggested by Mustakallio and Telkka. With these large doses necrosis of the proximal convolutions extended obviously beyond the terminal portions into almost all segments of the proximal convolutions. Inactivation of enzymatic activity in these necrotic tubules was complete after a few hours. In contrast, the ascending limbs of Henle's loops both located within the inner cortical zone and the outer portions of the medulla retained their full dehydrogenase activity. Superior preparations were obtained with thin frozen sections (about 10 μ) incubated in a buffered solution of neotetrazolium which contained, besides the sodium succinate, calcium chloride and sodium bicarbonate as activators. The use of blue tetrazolium with or without activators gave less satisfactory preparations. The results of our experiments would support our previously expressed view that the microscopically demonstrable effect of mercurial diuretics, even if given in very large amounts, is restricted to the proximal convoluted tubules (*3*).

M. WACHSTEIN
E. MEISEL

Laboratories of St. Catherine's Hospital
Brooklyn, New York

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Book Reviews

Reports on Progress in Physics, Vol. XVI. A. C. Stickland, Ed. London: Physical Society, 1953. 407 pp. Illus. + plates. 10s.

This sixteenth volume of the Physical Society's *Reports on Progress in Physics* maintains the high standards of the earlier volumes. The articles are written by experts in their respective fields, but do not require that the reader be a specialist in all the subjects covered. Each report is a useful review for workers in the field and, at the same time, helps the more casual reader in the almost hopeless task of keeping up with progress in physics.

The first five reports deal largely with different aspects of solid state physics and provide a broad summary of recent advances. The first article, Neutron Diffraction, by G. E. Bacon and K. Lonsdale, outlines the principles of neutron scattering by nuclei and magnetic atoms and discusses the fundamental experimental measurements. The applications of neutron diffraction techniques to the study of crystallography and solid-state physics are treated in some detail. The report Physical Properties and Atomic Arrangements in Crystals by W. A. Wooster is a survey of the relations between the magnetic, optical, piezoelectric, and elastic properties of crystals and their structural properties.

In the third article, Raman Effect in Solids, A. C. Menzies summarizes early work in this field and outlines recent advances in the theory of vibrations in crystals; work on the alkali halides is emphasized. Paramagnetic Resonance, by B. Bleaney and K. W. H. Stevens, deals with the theory and application of this particular branch of spectroscopy which has become increasingly important as a method of studying the solid state. The fifth article, Semiconductor Circuit Elements, by J. S. Blakemore, A. E. De Barr, and J. B. Gunn, reviews developments in the theory of conduction in semiconductors and semiconductor-metal systems, and discusses the properties and applications of these systems; the greatest emphasis is on silicon and germanium.

In Electrical Discharges, F. L. Jones deals particularly with the breakdown of gases in static fields, high-frequency discharges, cold emission phenomena in discharges, and the regime of space charges. The seventh article, Fluctuation Theory in Physical Measurements, by C. W. McCombie attempts to give a coherent, elementary account of the methods available for predicting the mean square errors introduced by fluctuations into different physical measurements. The eighth article, Cosmology, by W. H. McCrea, has to do with one of the most fascinating applications of physics—the study of the universe as a whole or of the large-scale properties of the universe. This review is especially interesting because of the way in which the nature, aims, principles, and methodology of the field are summarized.

The last report, The New Unstable Cosmic-Ray Particles, by G. D. Rochester and C. C. Butler, is a description of the properties of the newly discovered unstable particles with masses between 400 and 2200 electron masses. This excellent article makes clear many of the experimental results which seemed weird and scarcely believable in the original journal articles. The beautiful and clearly explained cloud-chamber and photographic emulsion pictures should serve as models for other workers in this field who wish to make their findings understood by the innocent.

IRVING KAPLAN

Reactor Physics Devision
Brookhaven National Laboratory

General Biochemistry. Joseph S. Fruton and Sofia Simmonds. New York: Wiley; London: Chapman & Hall, 1953. 940 pp. Illus. $10.00.

This textbook is designed for use in graduate courses in biochemistry. It presents a dynamic view of intermediary metabolism with emphasis on mechanisms. Illustrative material is taken from plants, animals, or microorganisms as needed and without prejudice. The word general in the title has the same sense as its usage in "general physiology."

After a brief historical introduction there are six chapters devoted to the physical properties, chemical constitution and structure of the various categories of simple and conjugated proteins. The next three chapters are concerned with the chemical properties of enzymes and with the thermodynamics and kinetics of enzyme catalyzed reactions. Then follow five chapters devoted to biological oxidation including discussion of the dehydrogenases, flavoproteins and metal containing oxidases. The opportunity is taken in this first part of the book to review those aspects of physical chemistry which are pertinent to biochemistry.

The next group of six chapters is concerned with carbohydrate chemistry, including the synthesis and degradation of polysaccharides, anaerobic, and aerobic metabolism of carbohydrates, and photosynthesis. The intermediary metabolism of lipids is covered in the following five chapters, including fats, phospholipids, steroids, carotinoids, terpenes, and anthocyanins. The next eight chapters are devoted to the intermediary metabolism of nitrogen compounds including inorganic compounds and nitrogen fixation, amino acids and proteins, porphyrins, and nucleic acids. The last few chapters serve to coordinate certain topics which would otherwise remain scattered as incidental facts throughout the text. Included here are the role of inorganic ions in metabolism, heat changes, hormonal control in plants, insects and mammals, and an integrated discussion of vitamins and growth factors.

The book is rich in structural formulas, schemes for metabolic pathways, and chemical equations. It contains for a textbook much tabulated quantitative data such as oxidation-reduction potentials, dissociation constants, and thermodynamic data for biologically

important substances. There are many footnote references to the literature, where possible to the most recent good review, and the volume has a competent subject index.

General Biochemistry can be heartily recommended as a textbook for courses devoted primarily to intermediary metabolism on a graduate level. There has been no text suitable for use in an advanced biochemistry course so that this book fills a very real need. It is not intended for courses in medical biochemistry or for use as a reference work. However, it is so up to date and covers such a broad range of biological topics that it might very well prove useful to any biological scientist as a handy desk reference to substances and processes of importance in intermediary metabolism.

MARK H. ADAMS

Department of Microbiology
New York University Bellevue Medical Center

The Earth: Its Origin, History, and Physical Constitution. 3rd ed. Harold Jeffreys. New York: Cambridge Univ. Press, 1952. 392 pp. + plates. $13.50.

This is the third edition of what is probably the most frequently quoted book on the interior of the earth. It is now twenty-four years since the second edition appeared. When it was written, the book was one of the first systematic attempts to put together the facts of astronomy, geodesy, and seismology to give a coherent picture of the interior of the earth. Perhaps the most remarkable thing about the new edition is its similarity to the last. The general framework has worn very well. The new results can be fitted into the previous scheme. They give it more detail and more certainty, but there has been no fundamental change. The earth still has a liquid core surrounded by a solid mantle. The crust still has a "granitic layer" and, rather more dubiously, an "intermediate layer." In detail, of course, there has been an enormous advance. The timetables of the seismic waves are now correct to about a second and the radius of the core is known with an uncertainty of a few kilometers. Rather surprisingly, progress has been least marked where it might be most expected, in explaining the processes of mountain building. Jeffreys still firmly supports his previous view that mountains are formed as a result of contraction. All his ingenuity is required to show that this is quantitatively adequate.

The book is little longer than the second edition. This miracle of compression has been achieved by omitting the chapters on the origin of the earth and by an admirable conciseness in the presentation. A geologist might perhaps feel that the elegance and generality of the treatment make a picture of an earth which is only rather distantly related to the one he knows, but it is certain that everyone who is interested in the structure and history of the earth will have this book on his shelves even if he has doubts about his ability to profit from the more esoteric passages such as the appendix on Castigliano's theorem.

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New Books

Léon Fredericq: Un Pionnier de la Physiologie. Oeuvres choisies. Paris: Masson, 1953. 232 pp. Illus. 1.345 fr.

Reptiles and Amphibians. A guide to familiar American species. Herbert S. Zim and Hobart M. Smith; illus. by James Gordon Irving. New York: Simon and Schuster, 1953. 157 pp. Illus. $1.50.

Quackery in the Public Schools. Albert Lynd. Boston: Little, Brown, 1953. 282 pp. $3.50.

Steps in Psychotherapy: Study of a case of sex-fear conflict. John Dollard, Frank Auld, Jr., and Alice Marsden White: Dael Wolfle, Ed. New York: Macmillan, 1953. 222 pp. $3.50.

A Brief Course in Semimicro Qualitative Analysis. William E. Caldwell and G. Brooks King. New York: American Book, 1953. 163 pp. $2.10.

General Chemistry. An introduction to descriptive chemistry and modern chemical theory. 2nd ed. Linus Pauling. San Francisco, Calif.: Freeman, 1953. 710 pp. Illus. + plates. $6.00.

Mathematical Methods for Scientists and Engineers. Lloyd P. Smith. New York: Prentice-Hall, 1953. 453 pp. Illus. $10.00.

Animal Biochromes and Structural Colours. Denis L. Fox. New York: Cambridge Univ. Press, 1953. 379 pp. Illus. + plates. $11.00.

Fabricated Materials and Parts. Theodore C. DuMond. New York: Reinhold, 1953. 332 pp. Illus. $6.50.

Living with a Disability. Howard A. Rusk and Eugene J. Taylor. New York: Blakiston, 1953. 207 pp. Illus. $3.50.

Cocoa: Cultivation, Processing, Analysis. Vol. III of *Economic Crops*; Z. I. Kertesz, Ed. Eileen M. Chatt. New York–London: Interscience, 1953. 302 pp. Illus. $8.50.

Annual Report of the Board of Regents of the Smithsonian Institution, 1952. Showing the operations, expenditures, and condition of the Institution for the year ended June 30. Washington, D. C.: Government Printing Office, 1953. 461 pp. Illus. + plates. $2.75.

Symposia of the Society for Experimental Biology, No. VII; ***Evolution.*** R. Brown and J. F. Danielli, Eds. New York: Academic Press, 1953. (For the Company of Biologists on behalf of the Society for Experimental Biology.) 448 pp. Illus. + plates. $7.80.

Historical Aspects of Organic Evolution. Philip G. Fothergill. New York: Philosophical Library, 1953. 427 pp. $6.00.

Laboratory Exercises for General Botany. Herbert M. Clarke and Richard I. Evans. Minneapolis, Minn.: Burgess, 1953. 104 pp. Illus. $1.50.

Mathematics and Statistics for Economists. Gerhard Tintner. New York: Rinehart, 1953. 363 pp. Illus. $6.50.

Heredity in Health and Mental Disorder. Principles of psychiatric genetics in the light of comparative twin studies. Franz J. Kallmann. New York: Norton, 1953. 315 pp. Illus. $6.00.

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Society for American Archaeology

New Affiliate of the American Association for the Advancement of Science

THE formal existence of the Society for American Archaeology began on December 28, 1934, when an organizational meeting following the annual dinner of Section H of the AAAS accepted a proposed constitution and elected a slate of officers. The institutional predecessor of the Society was the Committee on State Archaeological Surveys, created in 1921 by the National Research Council and later given financial aid by the Carnegie Corporation. Formation of the Society was the outgrowth of a need for better communication among archaeologists working in the Americas and for an effective method of informing the public of the unique character and scientific value of archaeological sites in order to prevent irresponsible destruction of the materials. Provision was made in the original constitution for a quarterly journal, annual meetings, and establishment of regional divisions. The objectives of the Society are set forth in Article II of the constitution:

Section 1. The objects of the Society shall be to promote and to stimulate interest and research in the archaeology of the American continents; to encourage a more rational public appreciation of the aims and limitations of archaeological research; to serve as a bond among those interested in American Archaeology, both professionals and non-professionals, and to aid in directing their efforts into more scientific channels; to publish and to encourage the publication of their results; to foster the formation and welfare of local archaeological societies; to advocate and to aid in the conservation of archaeological data; and to discourage commercialism in the archaeological field and to work for its elimination.

Section 2. The practice of collecting, hoarding, exchanging, buying or selling archaeological materials for the sole purpose of personal satisfaction or financial gain, and the indiscriminate excavation of archaeological sites are declared contrary to the ideals and objects of the Society.

A most important regular activity of the Society is the publication of *American Antiquity*, a quarterly journal devoted to technical articles, book reviews, and notes on American archaeology. Memoirs of the Society are issued at irregular intervals; nine have been published at the present time. Annual meetings are held in May of each year. The constantly growing number of papers submitted for presentation has led in recent years to a three-day session. Special meetings are frequently held in conjunction with other scientific meetings such as those of the AAAS and the American Anthropological Association. Another annual activity is the nomination of a recipient for the Viking Fund Medal and Award for Archaeology; this award is presented yearly by the Wenner-Gren Foundation for Anthropological Research, Inc. on the recommendation of the Society.

Several individual projects have been carried on from time to time as a result of special problems that have arisen. An example is the appointment of a Planning Committee in 1944 for the purpose of appraising the status of the unpublished materials accumulated by the many archaeological projects carried on by various relief agencies and making appropriate recommendations leading to their utilization. Subsequent establishment of the Smithsonian River Basin Surveys proved to be a satisfactory solution, and the Committee was dismissed.

Officers of the Society are: pres., Gordon F. Ekholm, associate curator of archaeology, American Museum of Natural History; 1st v. pres., George I. Quimby, Jr., curator of exhibits, Department of Anthropology, Chicago Natural History Museum; 2nd v. pres., Isabel Kelly, Reforma 34, Mexico, D.F., Mexico; sec., James B. Griffin, director, Museum of Anthropology, University of Michigan; treas., Richard B. Woodbury, associate professor of anthropology, Columbia University; editor, Jesse D. Jennings, professor of anthropology, University of Utah. The representative to the AAAS Council is Douglas S. Byers, Phillips Academy, Andover, Mass.

Membership in the Society as of April 18, 1953, included 224 institutional members and 901 individual members.

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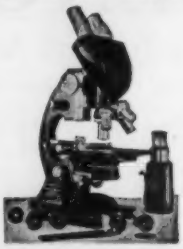

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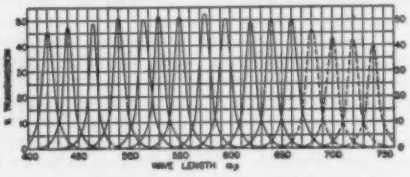

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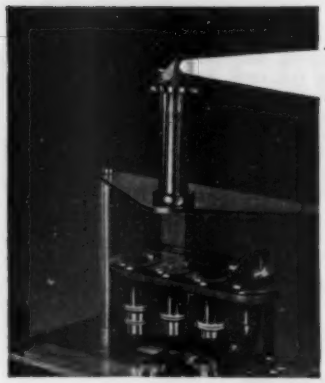

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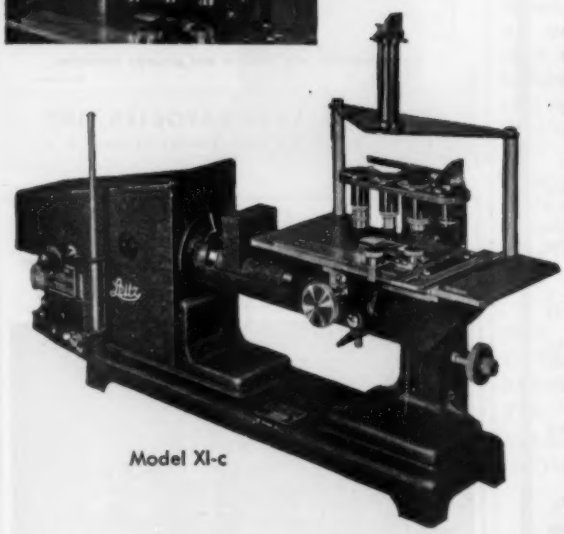

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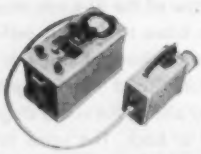

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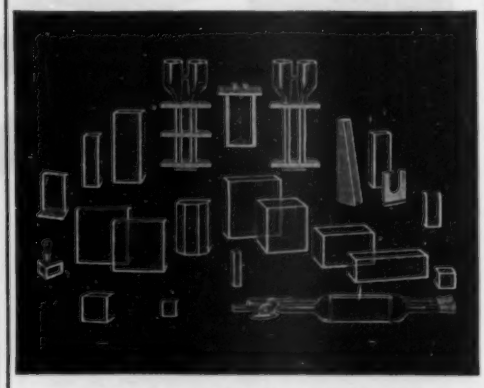

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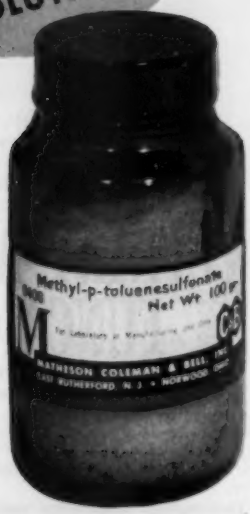

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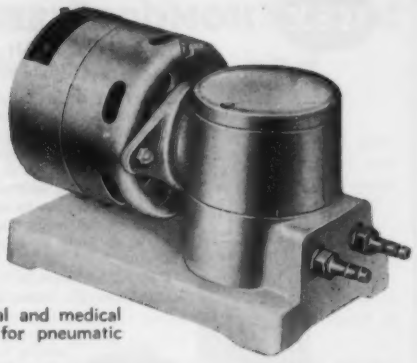

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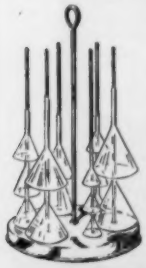

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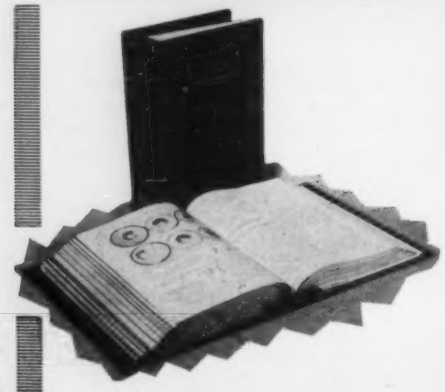

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29–30. Conf. on Protein Metabolism, 10th, New Brunswick, N.J. (W. H. Cole, Rutgers Univ., New Brunswick.)

29–30. Western Soc. for Clinical Research, 7th annual, Portland, Ore. (H. N. Hultgren, Stanford Hospital, San Francisco 15, Calif.)

February

1–3. American Acad. of Allergy, 10th annual, Houston, Tex. (Executive Office, 208 E. Wisconsin Ave., Milwaukee 2, Wis.)

1–5. American Soc. for Testing Materials, Spring, Washington, D.C. (R. J. Painter, 1916 Race St., Philadelphia 3, Pa.)

4. Instrument Soc. of America, Regional Conference, 9th annual, New York City. (L. Butzman, 103 Park Ave., New York, N.Y.

4–6. American Soc. for Quality Control, Textile Quality Control Conf., 4th annual, Raleigh, N.C. (D. Shainin, 70 E. 45 St., New York, N.Y.)

4–6. Inst. of Radio Engineers Conf. and Electronic Show, Tulsa, Okla. (D. R. Davis, P.O. Box 7221, Tulsa.)

5–6. Chicago Ophthalmology Soc., annual clinical, Chicago, Ill. (F. W. Newell, 950 E. 59 St., Chicago 37.)

7. Assoc. for Research in Ophthalmology, Midwest Section annual, Chicago, Ill. (F. W. Newell, 950 E. 59 St., Chicago 37.)

8–9. Conf. on Marine Corrosion Problems, Berkeley, Calif. (Dept. of Conferences and Special Activities, Univ. of California, Berkeley.)

12–25. Latin American Cong. of Oto-Rhino-Laryngology, 3rd, Caracas, Venezuela. (V. Marquez Reverson, Centro Medico, Caracas.)

13–14. American Educational Research Assoc., Atlantic City, N.J. (F. W. Hubbard, 1201 16 St., NW, Washington, D.C.)

14–16. National Soc. of College Teachers of Education, Atlantic City, N.J. (C. E. Eggertsen, School of Education, Univ. of Michigan, Ann Arbor.)

15–18. American Inst. of Mining and Metallurgical Engineers, New York City. (E. H. Robie, 120 E. 41 St., New York 17.)

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15–20. Latin American Cong. of Physical Medicine, Medellin, Colombia. (C. L. de Victoria, 176 E. 71 St., New York 21, N. Y.)

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